Crescita e metabolismo osseo

aggiornamento: 22 ottobre 2015

	Calcium ions	**Phosphate ions**
Extracellular		
Concentration		
total, in serum	2.5×10^{-3} M	1.00×10^{-3} M
free	1.2×10^{-3} M	0.85×10^{-3} M
Functions	Bone mineral Blood coagulation Membrane excitability	Bone mineral
Intracellular		
Concentration	10^{-7} M	$1–2 \times 10^{-3}$ M
Functions	**Signal for:** • Neuron activation • Hormone secretion • Muscle contraction	• Structural role • High energy bonds • Regulation of proteins by phosphorylation

The physiology of calcium and the other minerals involved in its metabolism is complex and intimately tied in with the physiology of bone.

Five principal humoral factors are involved in maintaining plasma levels of calcium, magnesium and phosphate and coordinating the balance between these and their content in bone.

The transmembrane transport of these elements is dependent on a series of complex mechanisms that are controlled by these hormones.

The plasma concentration of calcium is initially sensed by a calcium-sensing receptor which then sets up a cascade of events that initially determines parathyroid hormone secretion and eventually results in a specific action within the target organs, mainly bone and kidney.

Allgrove J. Physiology of calcium, phosphate and magnesium. Endocr Dev. 2009;16:8-31.

Williams Textbook of Endocrinology, 12th ed
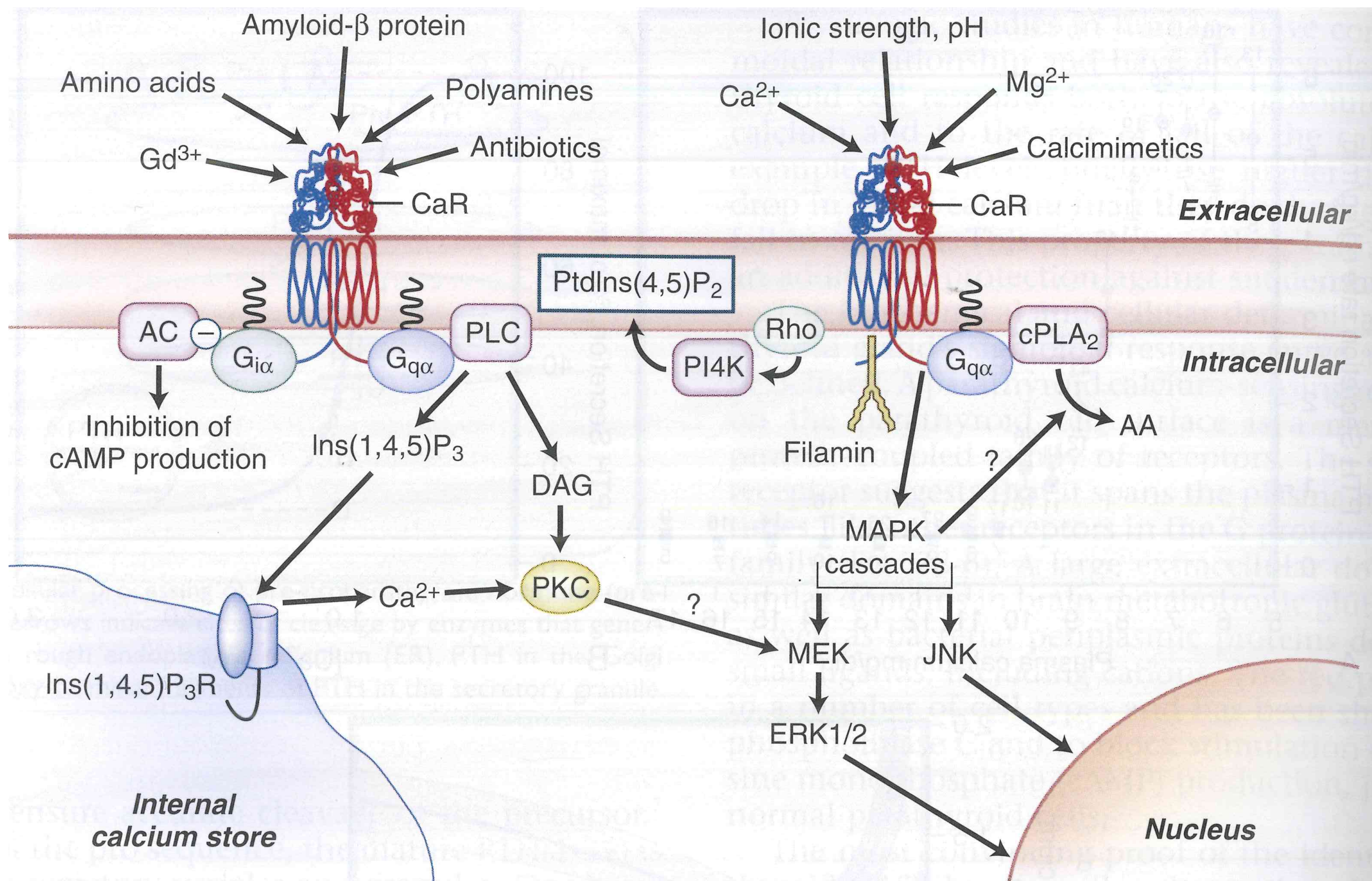
Calcium (Ca) and phosphorus (P) are the principal constituents of bone, and together they comprise 65% of its weight.

Bone, in turn, contains almost all of the calcium and phosphorus and more than half of the magnesium in the human body.

Ninety-nine percent of total body calcium resides in bone, of which 99% is located within the crystal structure of the mineral phase. Eighty-five percent of body phosphate is in the mineral phase of bone, and the remainder is located in inorganic or organic form throughout the extracellular and intracellular compartments.

Over the long run, maintenance of normocalcaemia takes precedence over skeletal integrity, hence bone is lost and mineralisation is suppressed at the expense of circulating concentrations until calcium sufficiency is restored.

Lieben L, Masuyama R, Torrekens S, et al. Normocalcemia is maintained in mice under conditions of calcium malabsorption by vitamin D-induced inhibition of bone mineralization. *J Clin Invest* 2012; **122:** 1803–15.
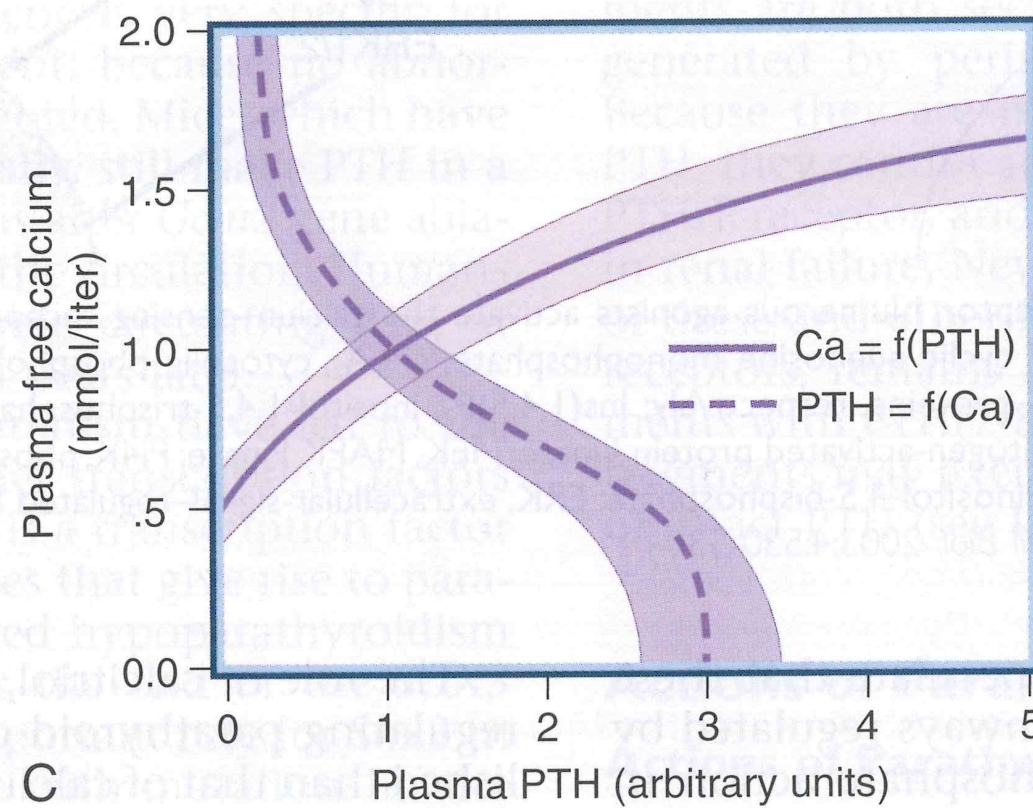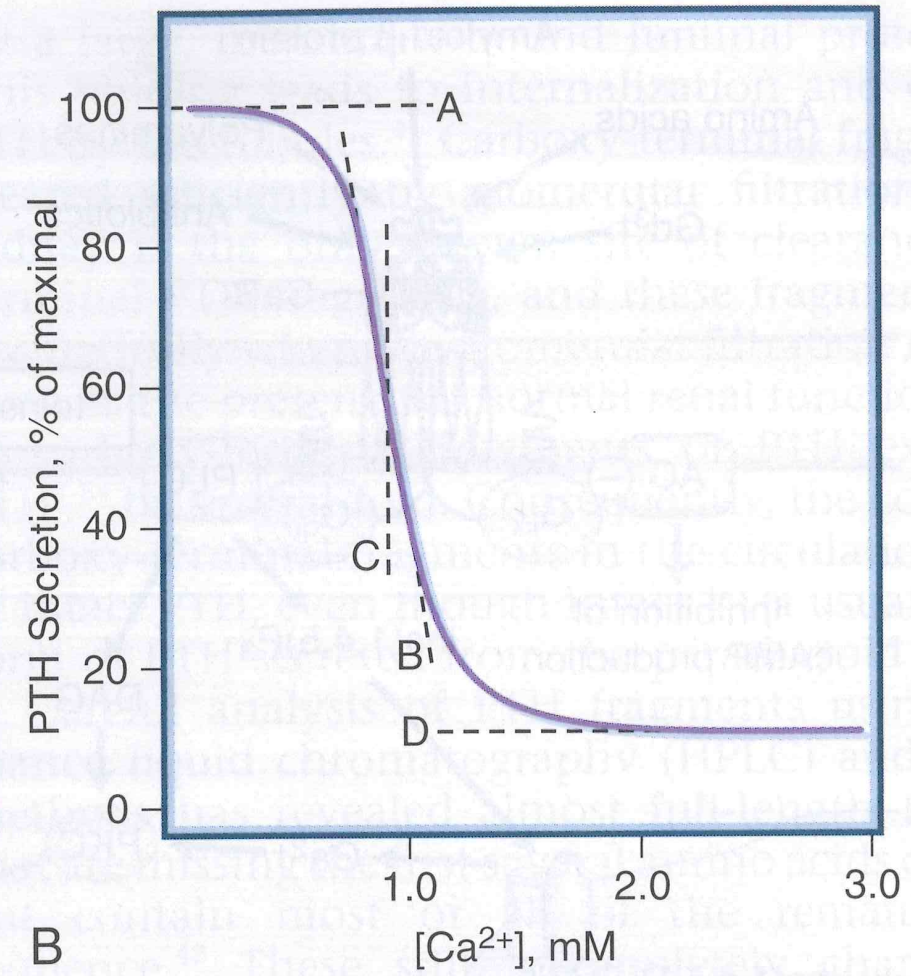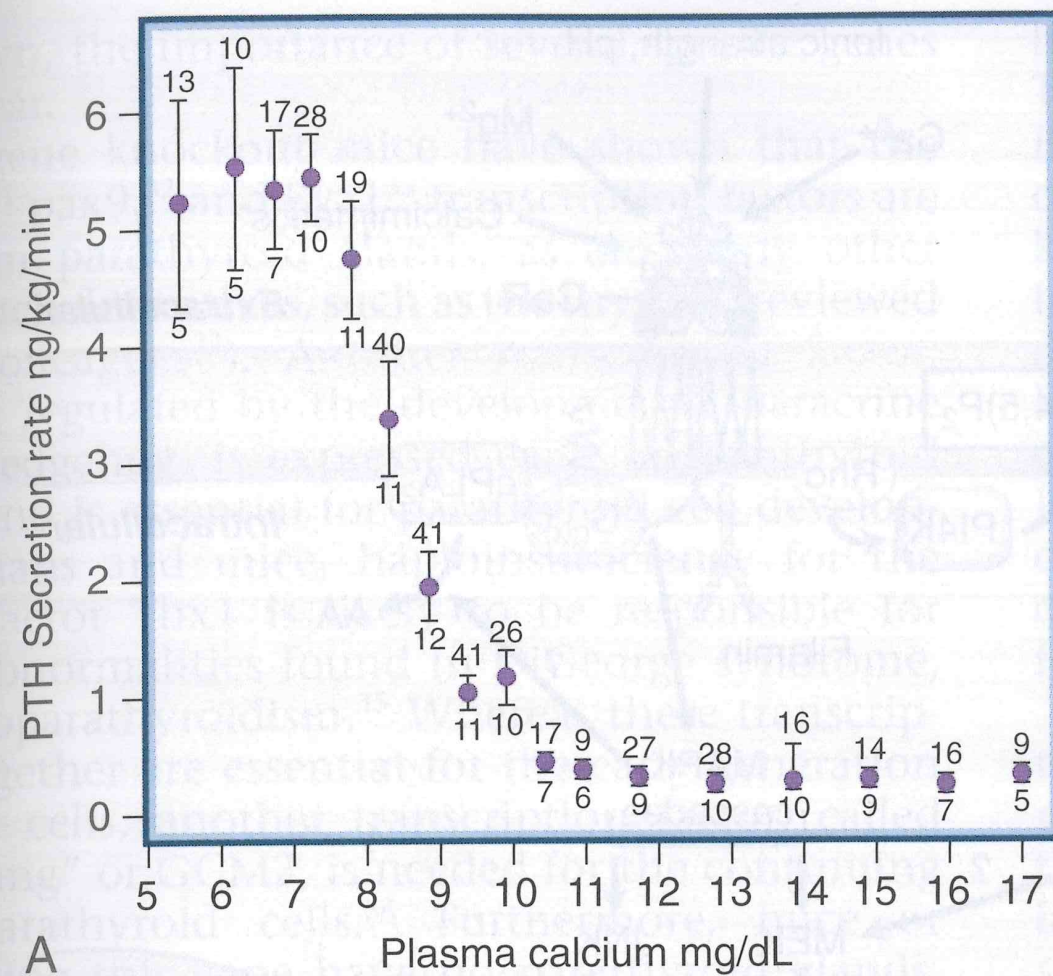
(Major) hormones involved in mineral ion homeostasis
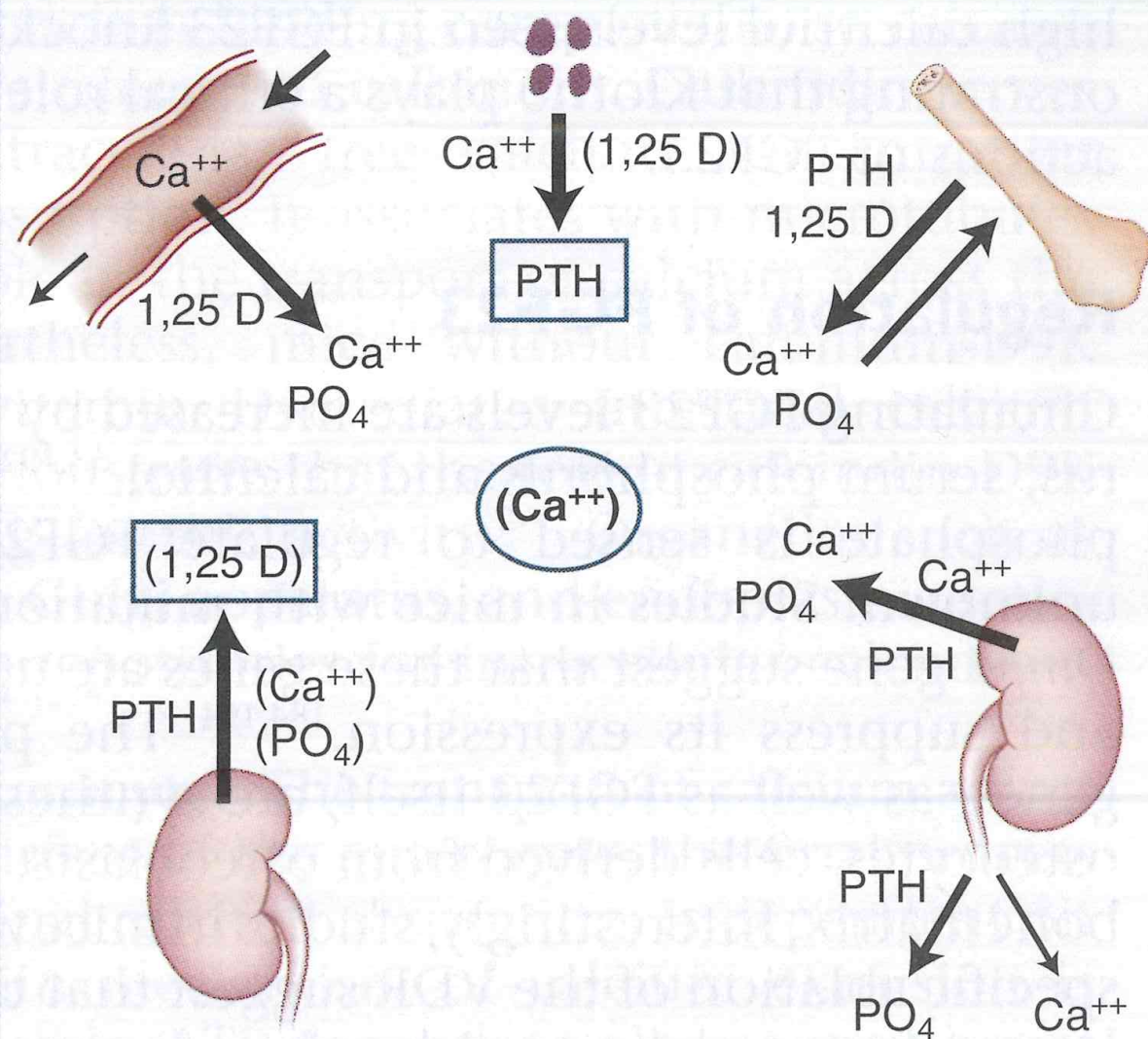
parathyroid hormone (PTH)

calcitonin

$1,25(OH)_2D_3$ (1,25-dihydroxyvitamin D or calcitriol)

fibroblast growth factor 23 (FGF23)

Williams Textbook of Endocrinology, 12th ed

Adaptation to dietary calcium deprivation

Adaptation to dietary calcium loading

Ca^{++}

Ca^{++} (1,25 D)

PTH
1,25 D

PTH

1,25 D

Ca^{++}
PO_4

PTH
1,25 D

Ca^{++}

Ca^{++} (1,25 D)

PTH
1,25 D

PTH

1,25 D

Ca^{++}
PO_4

PTH

PO_4

Ca^{++}

(Ca^{++})

(1,25 D)

PTH

(Ca^{++})
(PO_4)

Ca^{++}
PO_4

Ca^{++}

PTH

PTH

PO_4

Ca^{++}

(Ca^{++})

(1,25 D)

PTH

(Ca^{++})
(PO_4)

Ca^{++}
PO_4

Ca^{++}

PTH

PTH

PO_4

Ca^{++}

Williams Textbook of Endocrinology, 12th ed

2013 Masuyama vitD
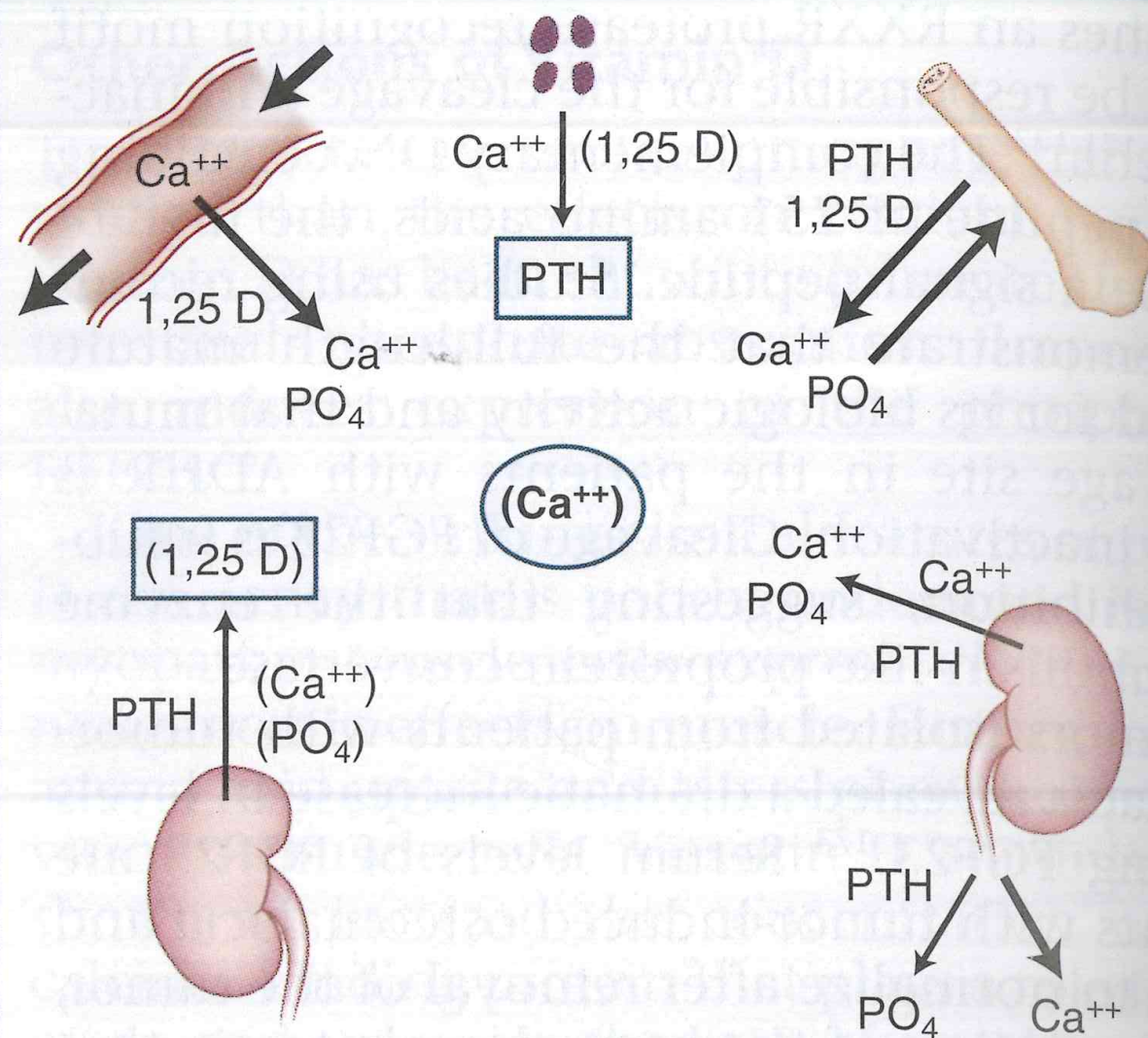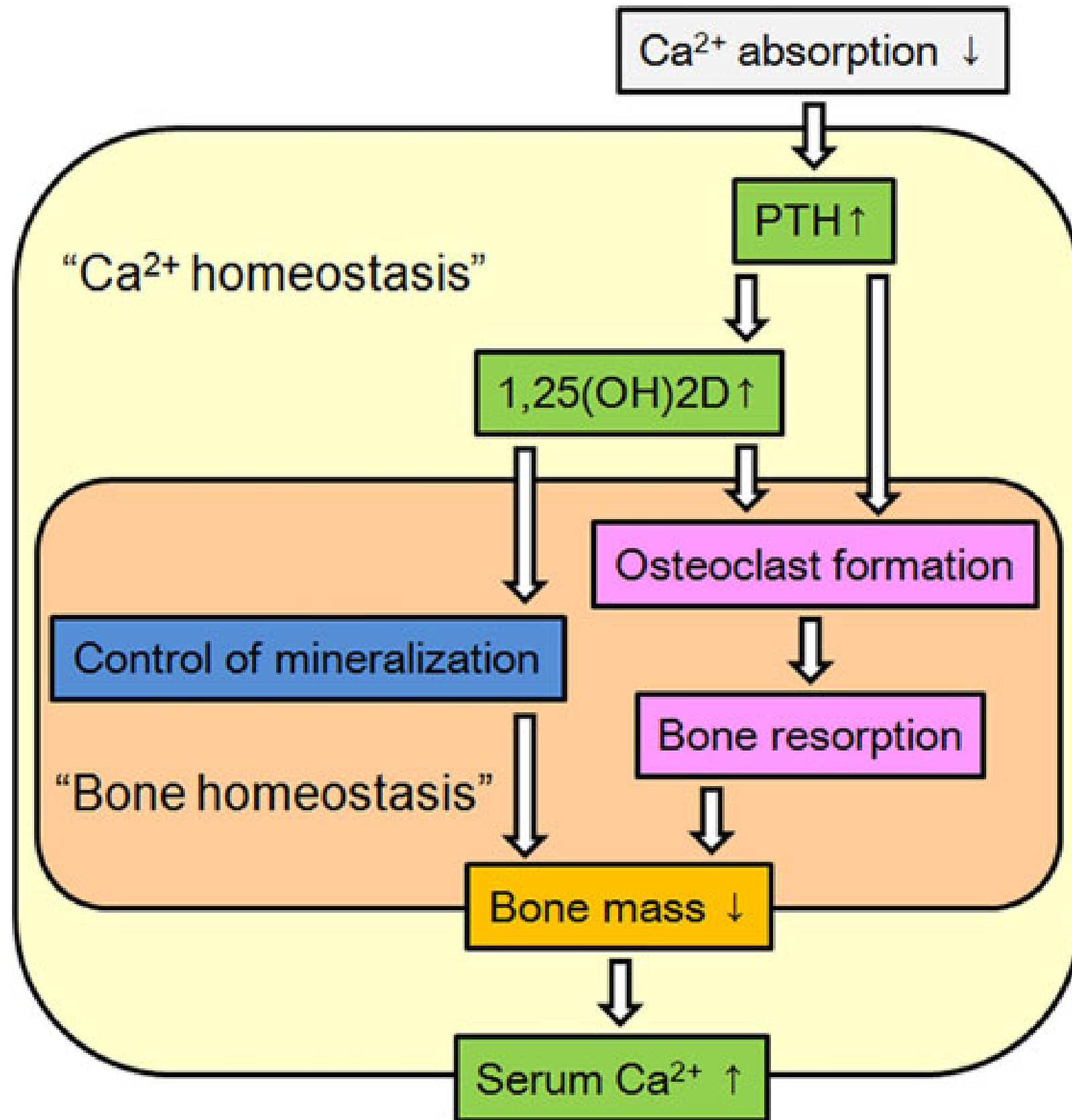
The Human skeleton

- complex organ
- 206 bones
- appendicular (126), axial (74), ossicles (6)
- functions
- 2 tissues, 3 cell types

1 - parietale
2 - temporale
3 - zigomatico
4 - mandibola
5 - clavicola
6 - costole
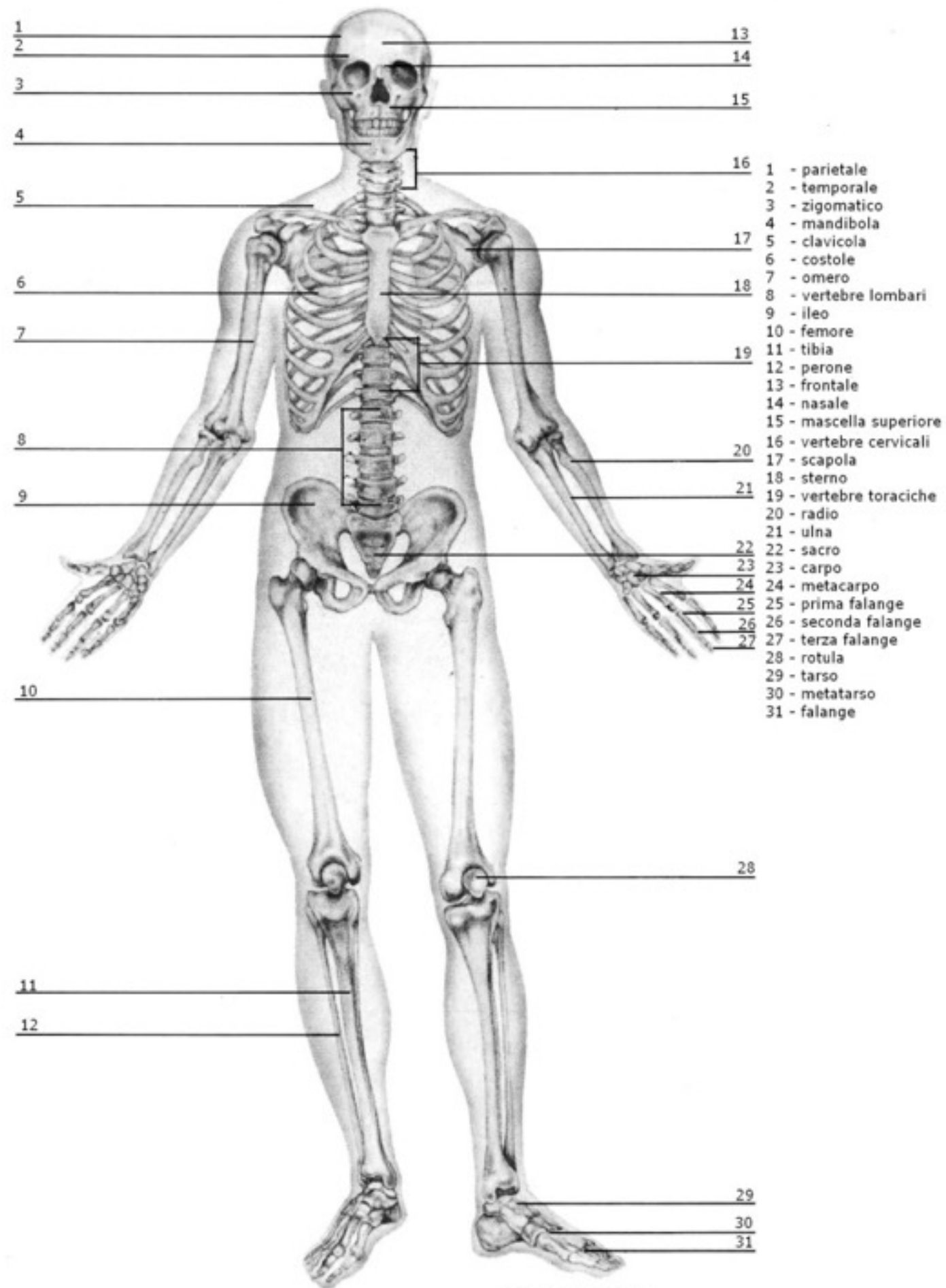7 - omero
8 - vertebre lombari
9 - ileo
10 - femore
11 - tibia
12 - perone
13 - frontale
14 - nasale
15 - mascella superiore
16 - vertebre cervicali
17 - scapola
18 - sterno
19 - vertebre toraciche
20 - radio
21 - ulna
22 - sacro
23 - carpo
24 - metacarpo
25 - prima falange
26 - seconda falange
27 - terza falange
28 - rotula
29 - tarso
30 - metatarso
31 - falange

Scheletro anteriore

FUNCTIONS OF BONE

- locomotion;
- mechanical support of the diaphragm and hence breathing;
- support and protection of the brain, spinal cord, heart, and lungs;
- support of hematopoiesis in the bone marrow;
- reservoir for minerals, in particular the regulation of calcium;
- repair of fractures and other bony defects;
- attachments for muscles, ligaments, and tendons.

Crescita in lunghezza
Crescita in massa

Table 664-2 **SKELETAL GROWTH CONSIDERATIONS**

- Abnormal stature can be assessed as "proportionate" or "disproportionate" based on comparing the ratio of sitting height with subischial height (lower limbs).

- Normally the arm span is almost equal to standing height.

  The head is disproportionately large at birth and ratio of head height to total height is approximately 1 : 4 at birth, which changes to 1 : 7.5 at skeletal maturity.

  Lower extremities account for about 15% of height at birth and 30% at skeletal maturity.

  The rate of height and growth increase is not constant and varies with growth spurts.

  Bone age is more important than chronological age in determining future growth potential.

Expert CONSULT

Nelson Textbook of PEDIATRICS

KLIEGMAN
STANTON
ST. GEME
SCHOR
BEHRMAN

Naissance	6 mois	1 an	2 ans	3 ans	4 ans	5 ans		6 ans	7 ans	8 ans	9 ans	10 ans	11 ans	12-13 ans

Età di comparsa dei nuclei di ossificazione
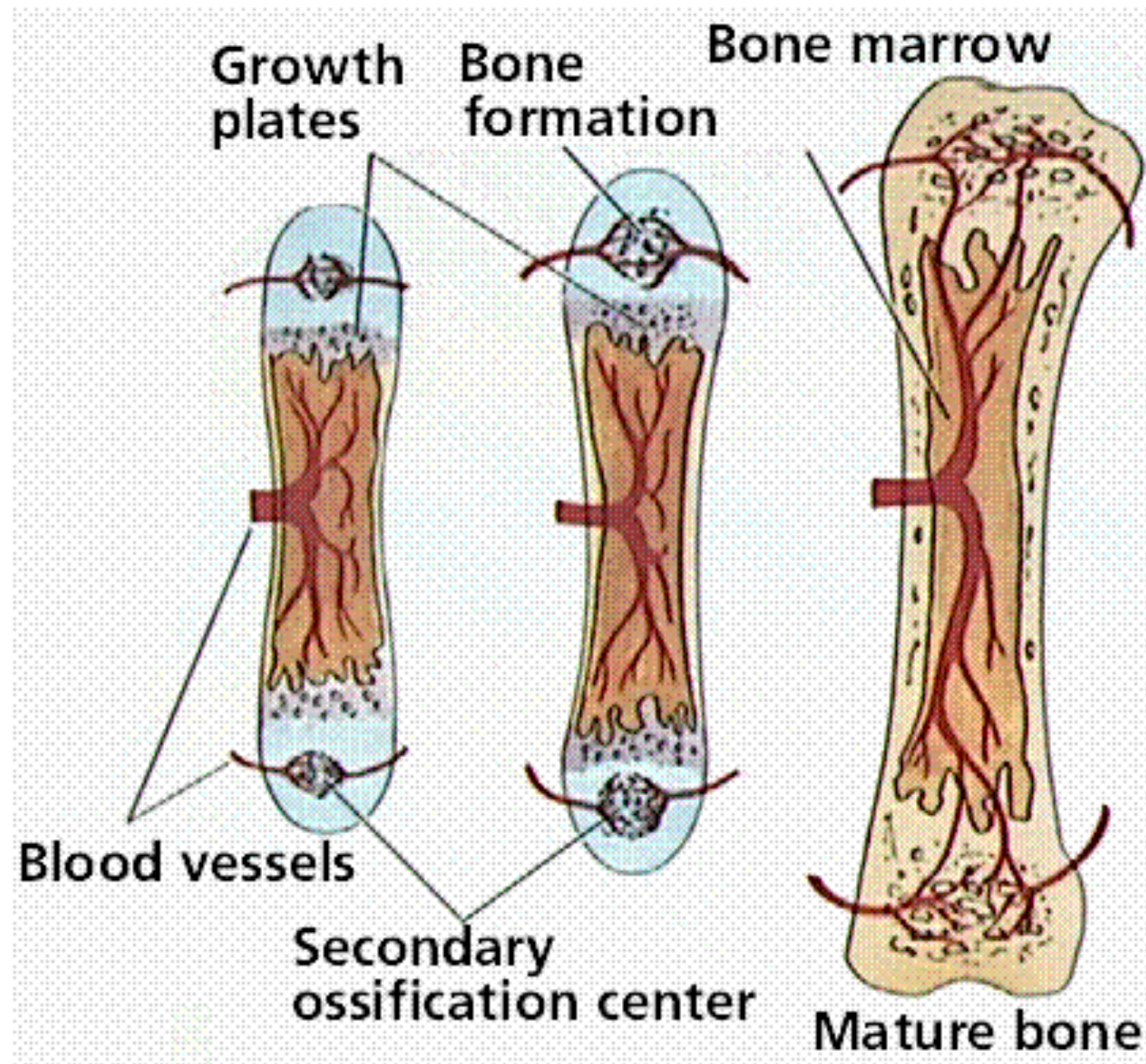
Expert|CONSULT

BONE FORMATION

- ENDOCHONDRAL
  - bones form from cartilage anlagen
  - complex process of chondrogenesis, hypertrophy, apoptosis, bone replacement
  - Major mechanism of skeletogenesis

- INTRAMEMBRANOUS
  - mesenchymal cells condense
  - tissue vascularizes
  - cells differentiate directly to osteoblasts
  - Flat skull bones, clavicles form this way
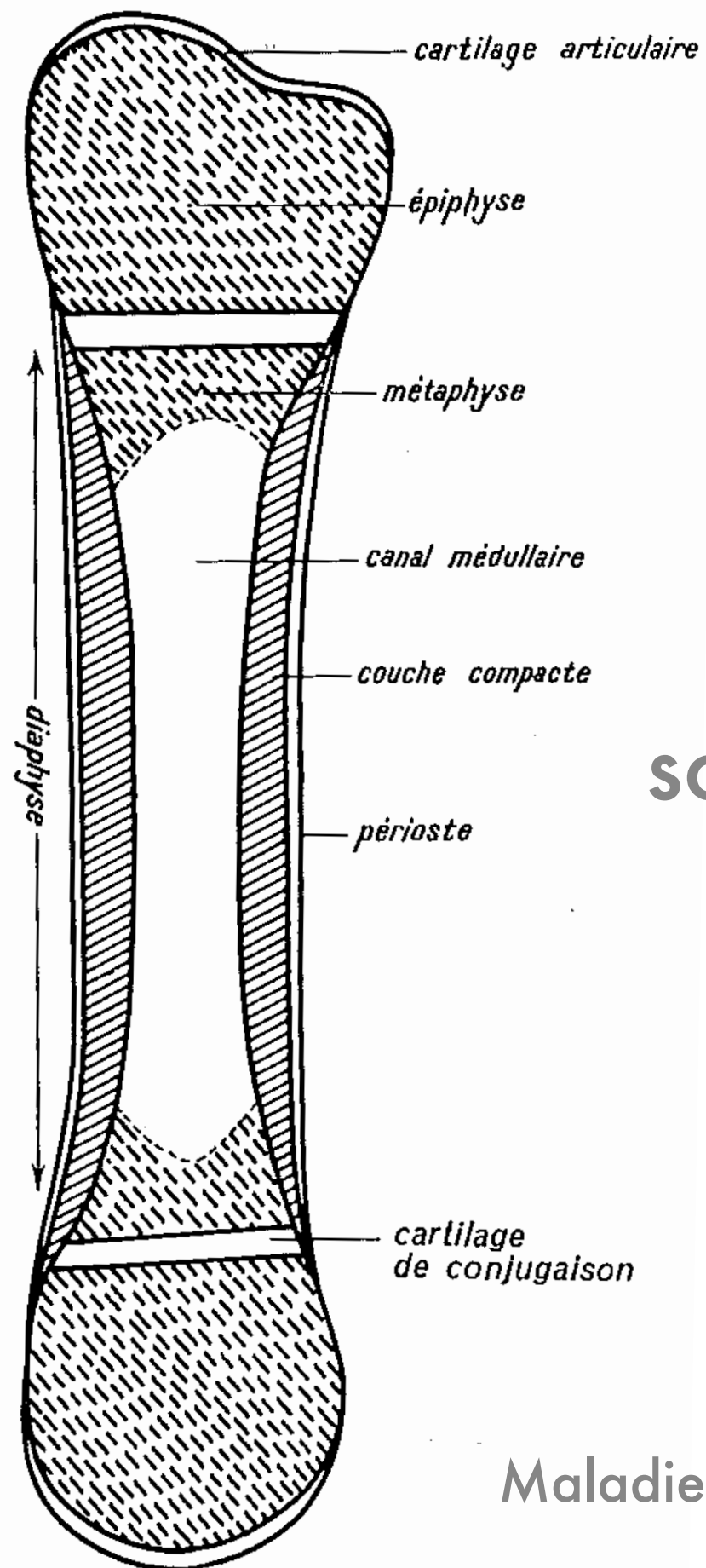
Endochondral ossification

Intramembranous ossification

Crescita in lunghezza

cartilage articulaire

épiphyse

métaphyse

canal médullaire

couche compacte

périoste

cartilage
de conjugaison

diaphyse

schema di un osso lungo

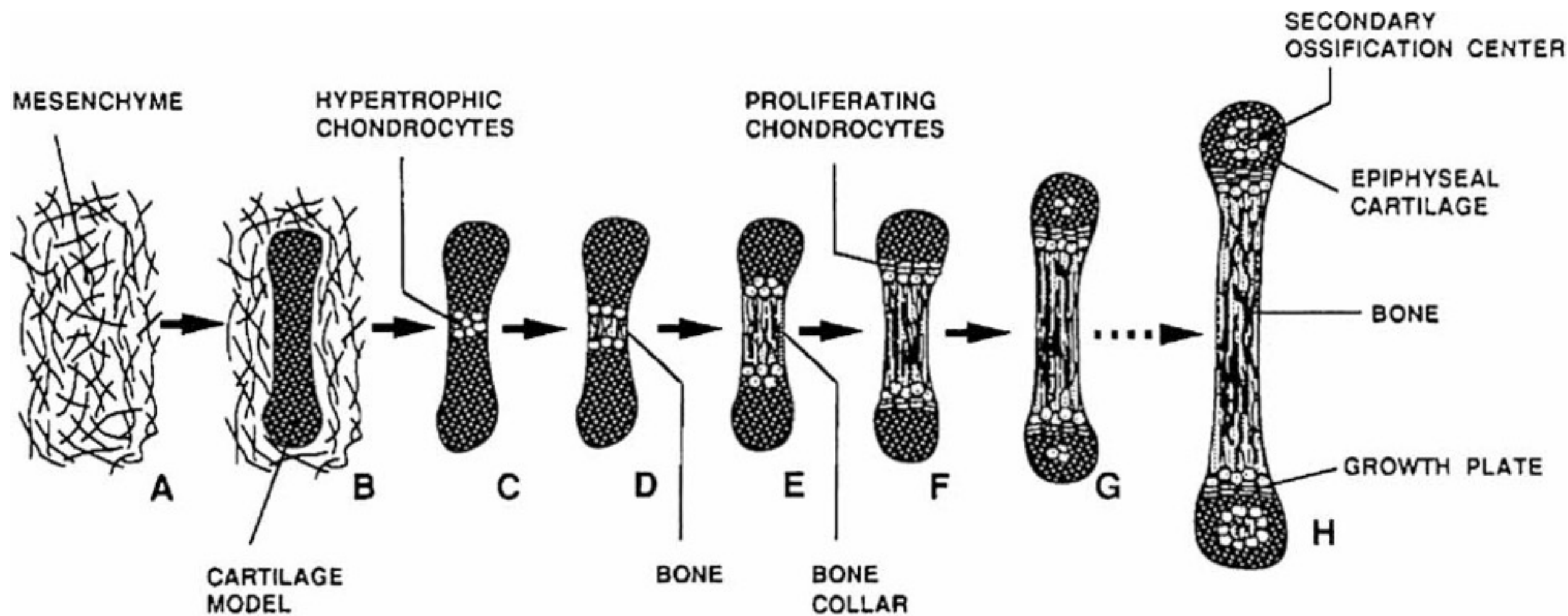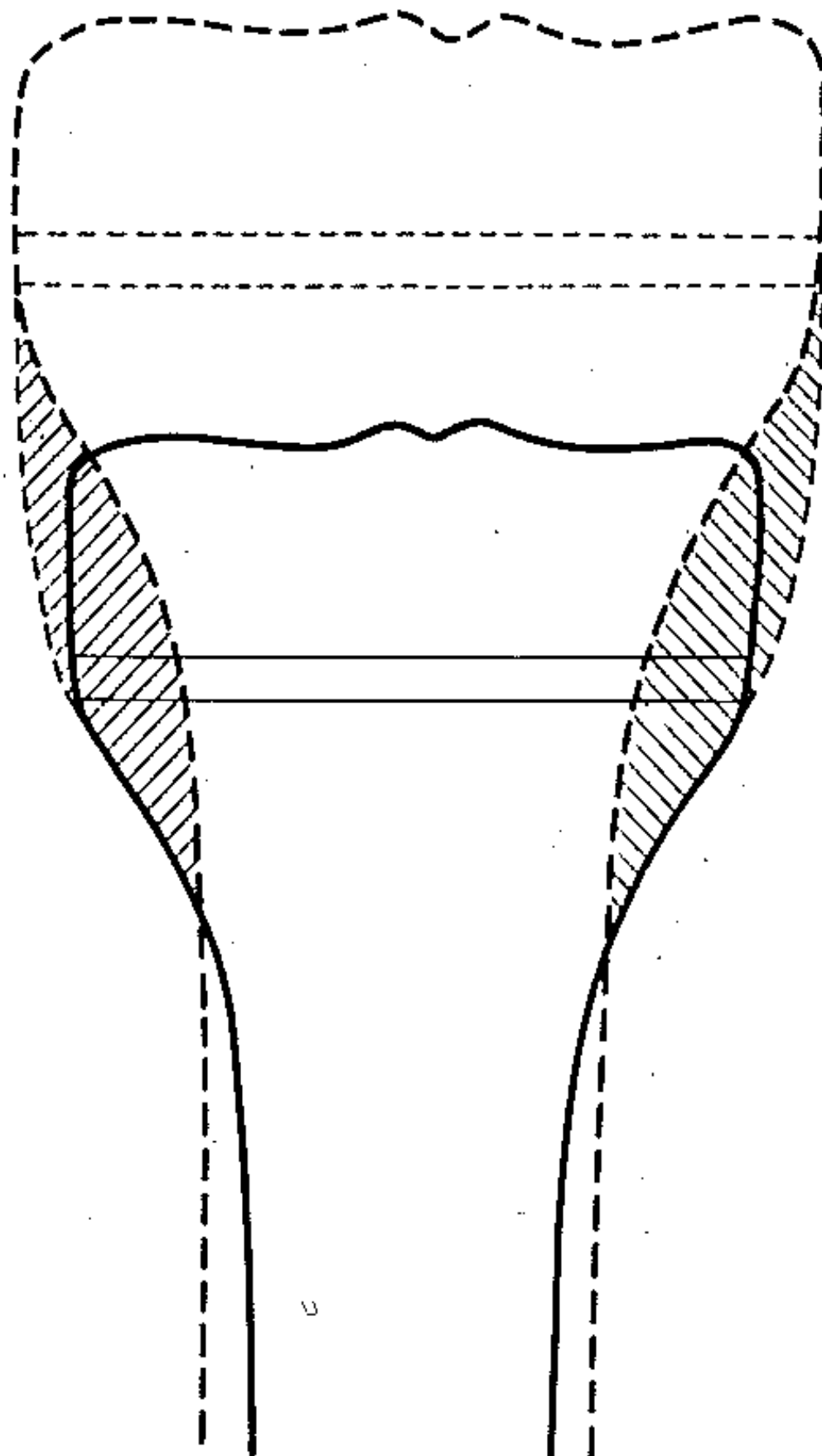Maroteaux P.
Maladies osseuses de l'enfant. Flammarion 2005
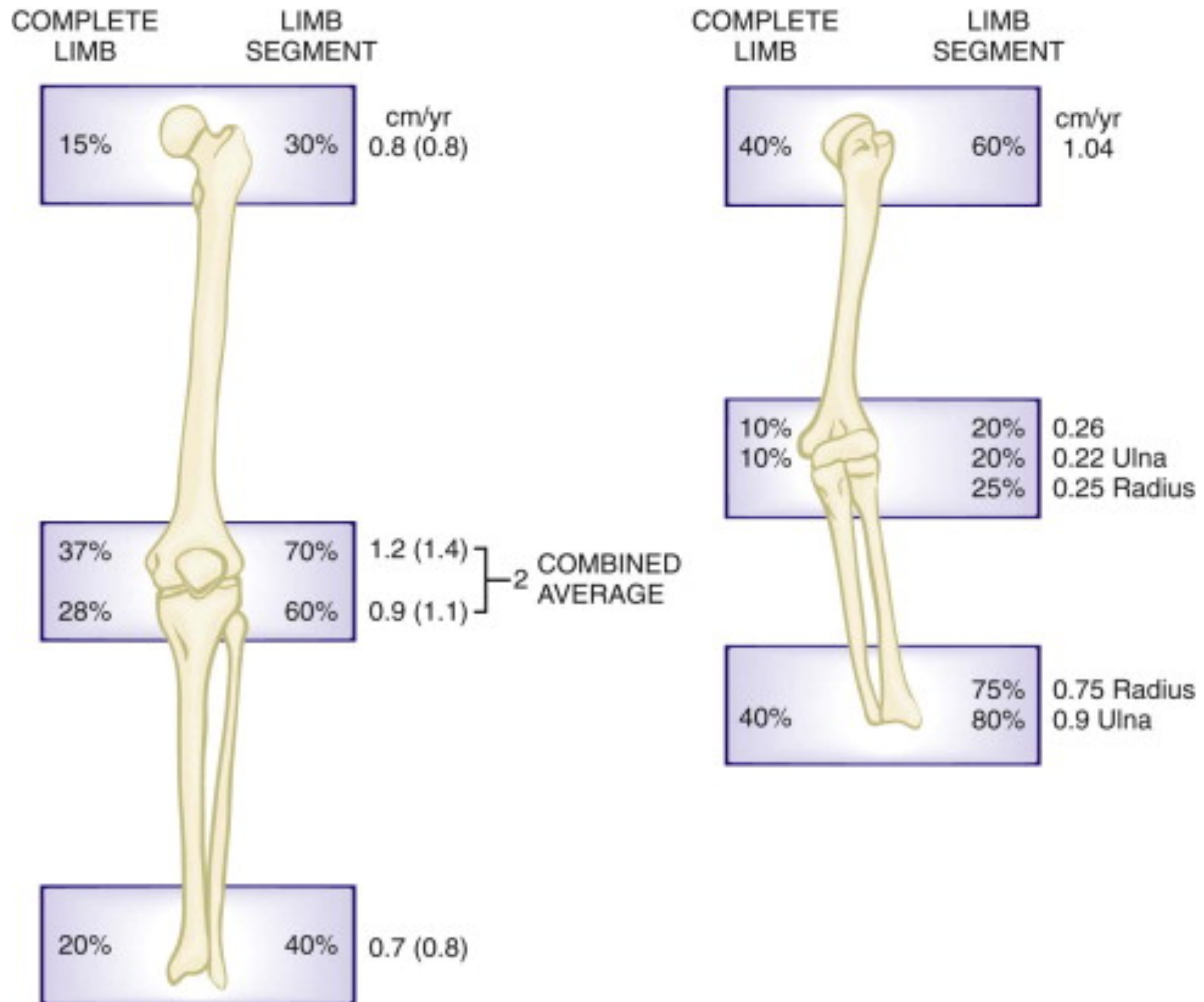
FIG. 6. Formation and growth of a long bone

Schema di modellamento osseo

Ossificazione
a livello vertebrale

Figure 664-2 The contribution (%) of each physis to the overall length of the extremities.
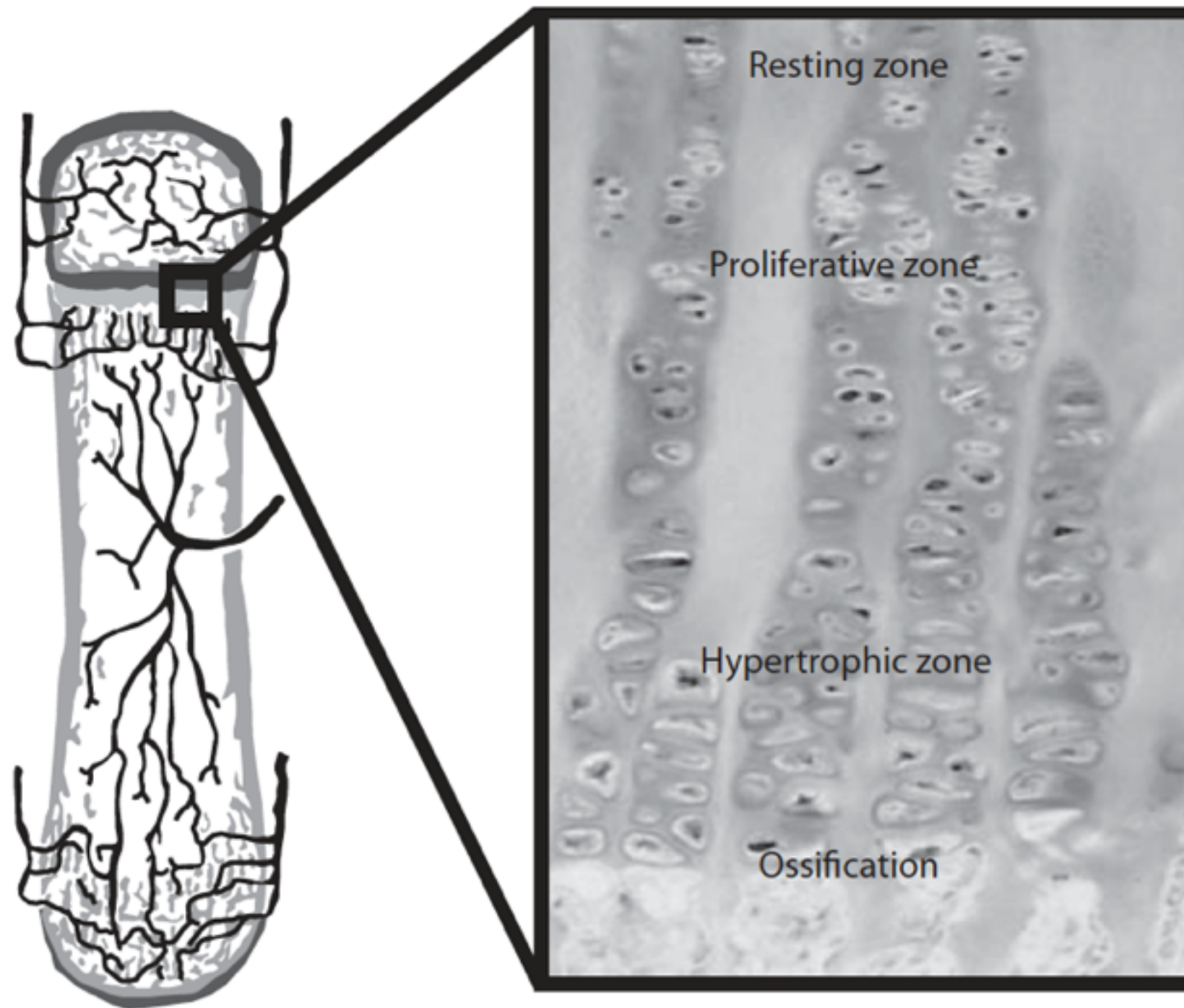
Type I Type II Type III

Type IV Type V

Resting zone

Proliferative zone

Hypertrophic zone

Ossification

Organization of the epiphyseal growth plate.
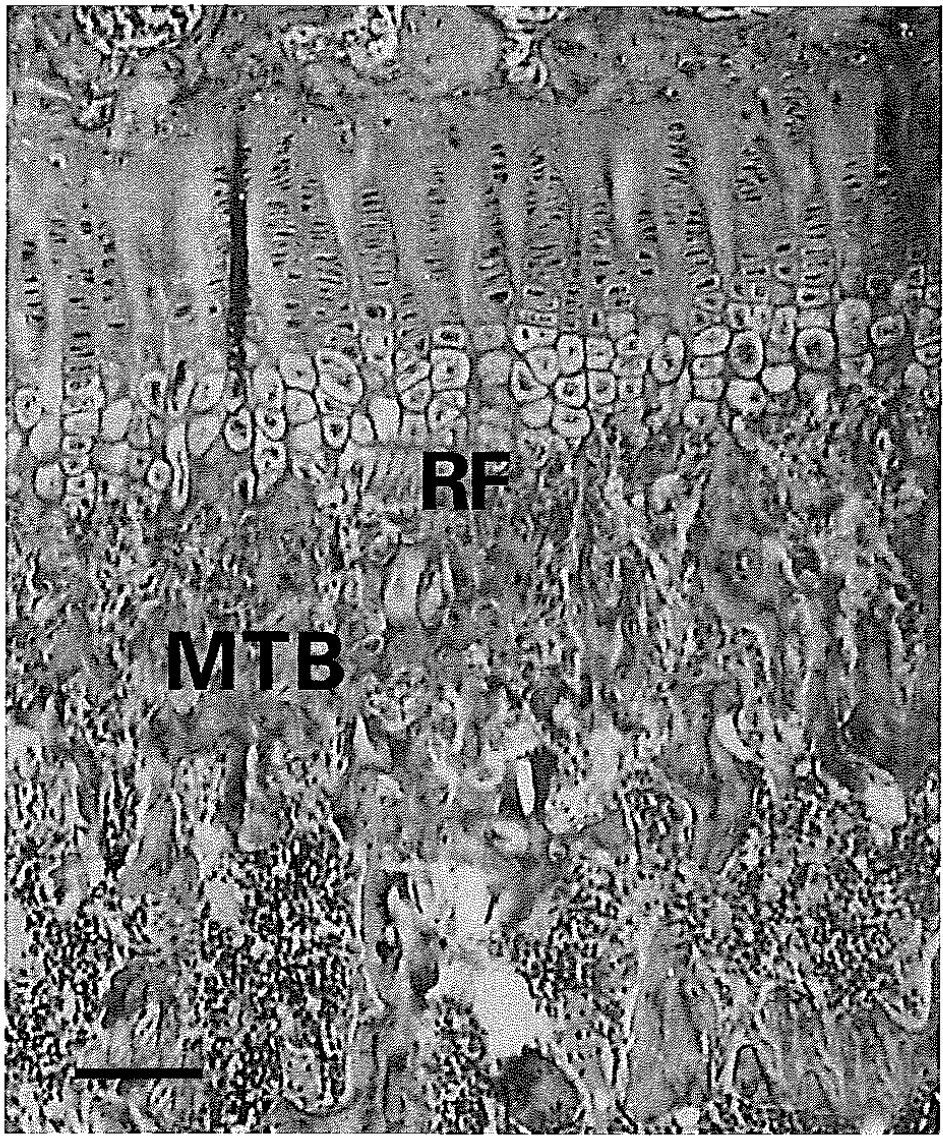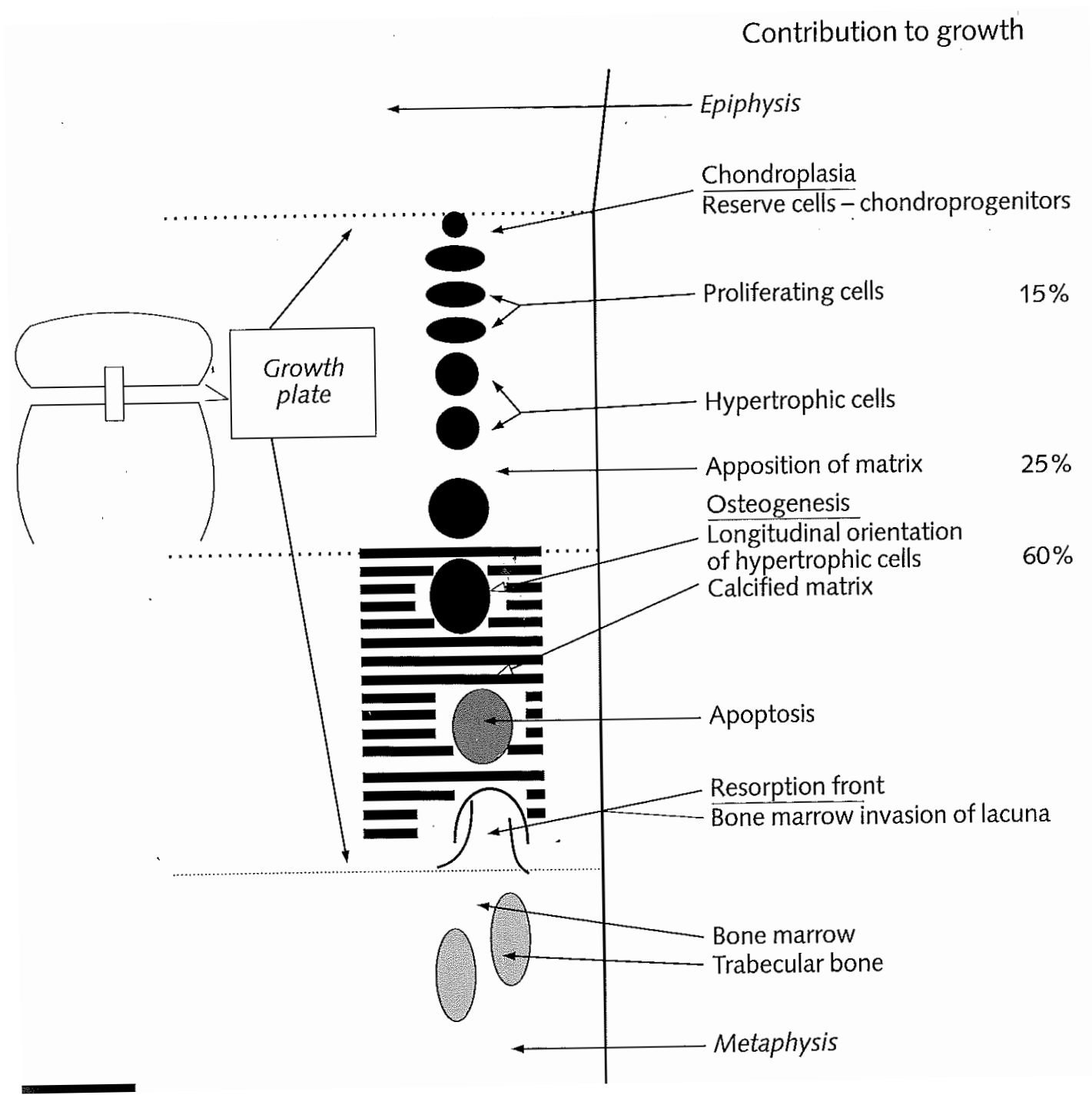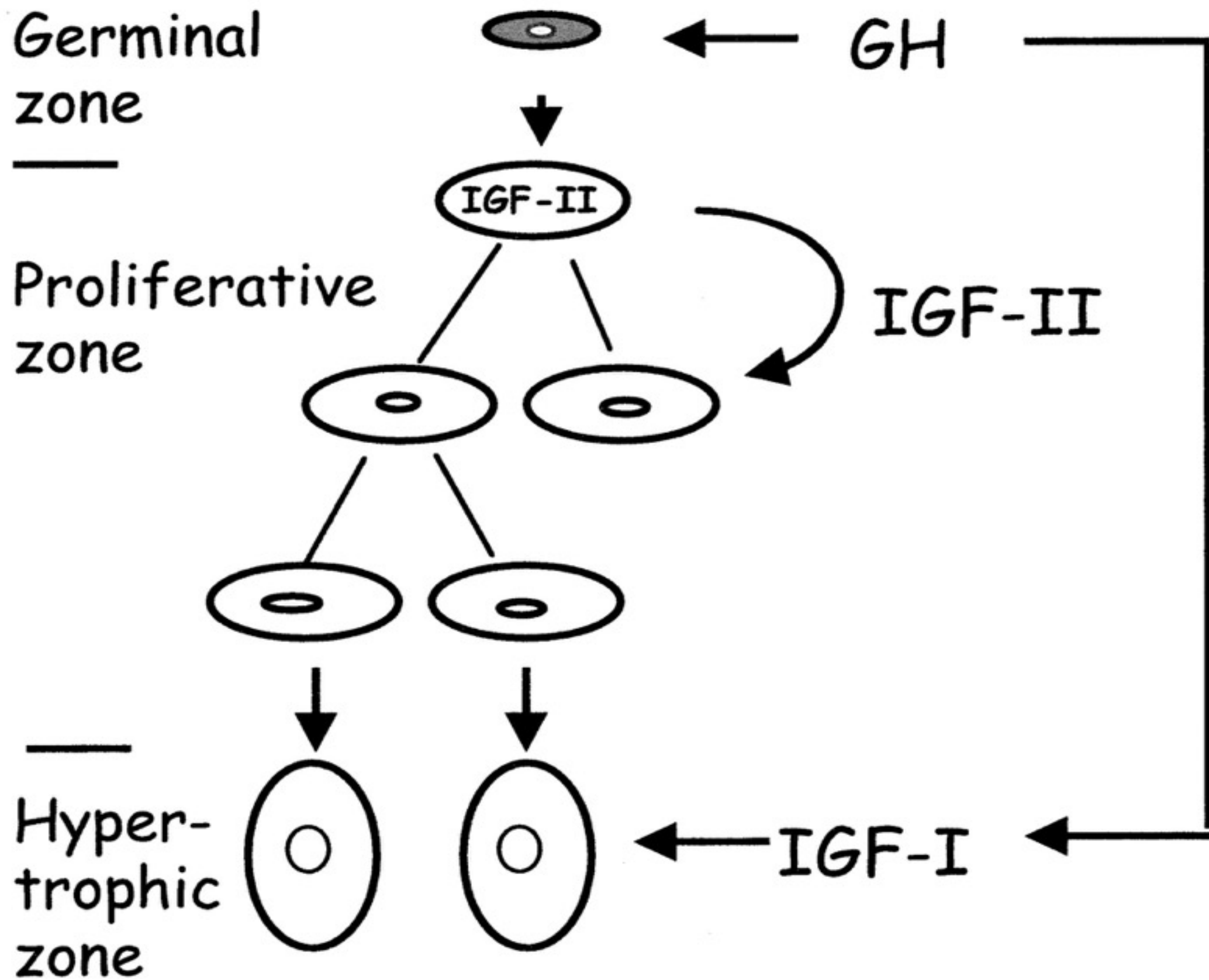
Contribution to growth

- Epiphysis

Chondroplasia
Reserve cells – chondroprogenitors

Proliferating cells   15%

Hypertrophic cells

Apposition of matrix   25%

Osteogenesis
Longitudinal orientation
of hypertrophic cells   60%
Calcified matrix

Apoptosis

Resorption front
Bone marrow invasion of lacuna

Bone marrow
Trabecular bone

- Metaphysis

Growth plate

RF

MTB

Germinal zone

Proliferative zone

Hyper-trophic zone

GH

IGF-II

IGF-II

IGF-I

Le Roith D et al. Endocr Rev 2001; 22: 53-74

**Growth Hormone, Insulin-Like Growth Factors, and the
Skeleton**

Andrea Giustina, Gherardo Mazziotti, and Ernesto Canalis

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Italy; Department of Research, Saint Francis Hospital and Medical Center (E.C.), Hartford, Connecticut 06105; and The
University of Connecticut School of Medicine (E.C.), Farmington, Connecticut 06030*

TABLE 1. Effects of GH on bone

Functions	Effects
Growth plate	
Replication of condrocytes	↑ ↑
Endochondral bone formation	↑ ↑
Bone remodeling unit	
Osteoblastogenesis	↑
Proliferation of osteoblasts	↑
Function of mature osteoblasts	↔ ↑
Production of osteoprotegerin	↑
Production of RANK-L	↔
Calcium metabolism	
Phosphate retention	↑

Effects of GH on bone. ↔ no effect; ↑ minor stimulating effect; ↑ ↑ major stimulating effect.

Growth Hormone, Insulin-Like Growth Factors, and the Skeleton

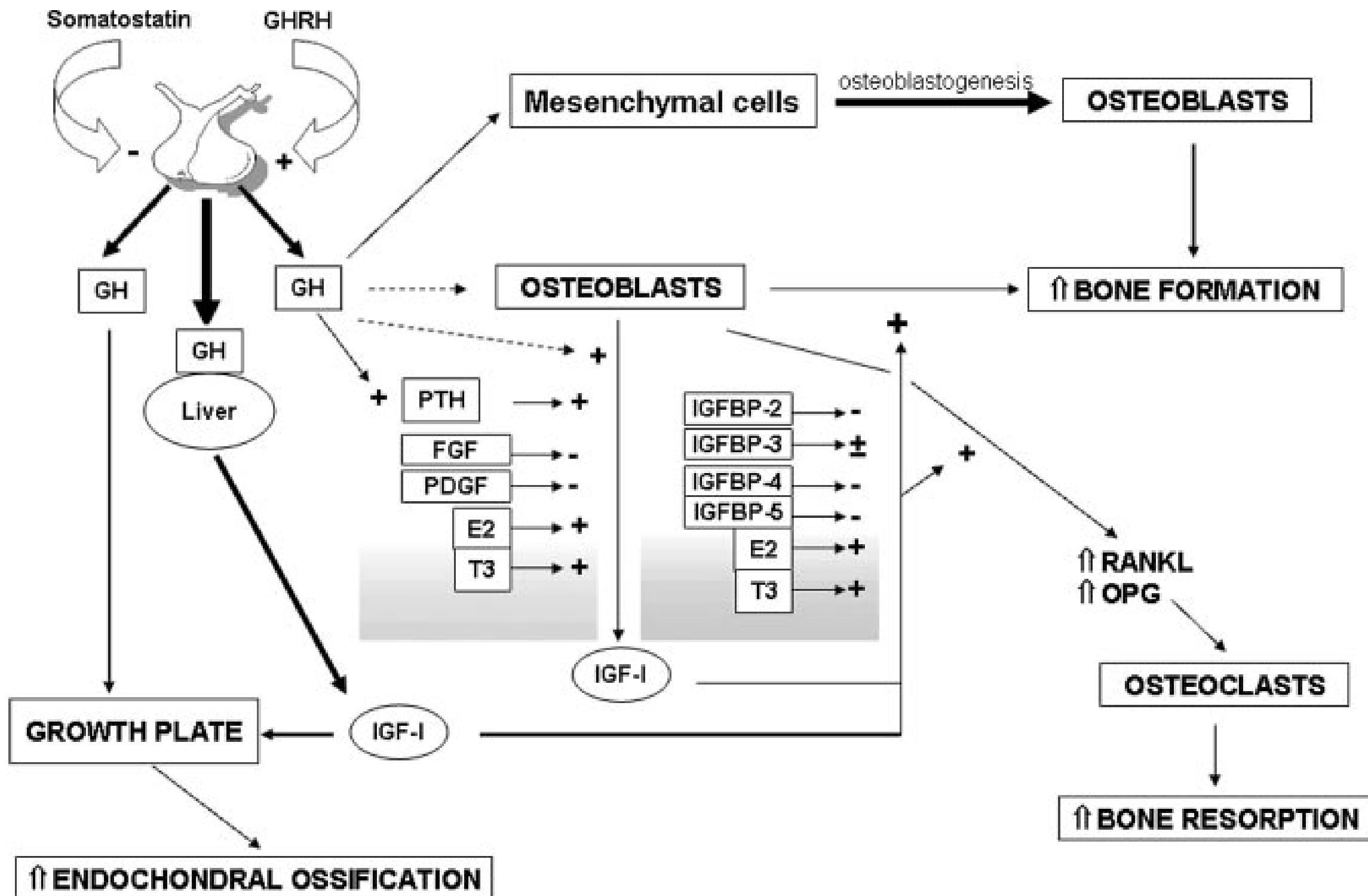Andrea Giustina, Gherardo Mazziotti, and Ernesto Canalis

Department of Medical and Surgical Sciences (A.G., G.M.), Chair of Internal Medicine, University of Brescia, 25125 Brescia, Italy; Department of Research, Saint Francis Hospital and Medical Center (E.C.), Hartford, Connecticut 06105; and The University of Connecticut School of Medicine (E.C.), Farmington, Connecticut 06030

- GH and IGF-I are important regulators of bone homeostasis and are central to the achievement of normal longitudinal bone growth and bone mass.

- Although GH may act directly on skeletal cells, most of its effects are mediated by IGF-I, which is present in the systemic circulation and is synthesized by peripheral tissues.

- The availability of IGF-I is regulated by IGF binding proteins.

- IGF-I enhances the differentiated function of the osteoblast and bone formation.

Growth Hormone, Insulin-Like Growth Factors, and the Skeleton

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Insulin-like Growth Factor-I and Bone

Daniel D. Bikle and Yongmei Wang

*Veterans Affairs Medical Center and University of California San Francisco,
San Francisco, California, USA*

1

- Insulin-like growth factor-I (IGF-I) is produced by chondrocytes, osteoblasts, osteocytes, and osteoclasts, and its receptor (IGF-IR) is found in all of these cells.

- The actions of IGF-I are mediated by IGF-IR, a tetrameric membrane-bound receptor homologous to the insulin receptor.

- When activated this receptor sets into motion two signaling pathways, the PI3K/Akt pathway and the Ras/Raf/MAPK/ERK pathway.

- Skeletal loading *in vivo* or of osteoblasts and osteocytes *in vitro* enhances IGF-I signaling by inducing IGF-I production and stimulating the interaction between IGF-IR and selected integrins that are critical for IGF-I signaling.

- The actions of IGF-I are regulated by the six IGF-binding proteins in both an inhibitory and stimulatory fashion. Different binding proteins have different actions often depending on the context of the experimental situation.

PERSPECTIVES

Insulin-like Growth Factor-I and Bone

Daniel D. Bikle and Yongmei Wang

Veterans Affairs Medical Center and University of California San Francisco, San Francisco, California, USA

2

- The relative contributions of circulating IGF-I (produced primarily in the liver) and that produced by bone remain in dispute, although both are involved in skeletal development.

- Cell-specific deletion of IGF-IR blunts chondrocyte and osteoblast proliferation and differentiation and inhibits osteoclastogenesis.

- IGF-I facilitates the skeletal actions of a number of calciotropic hormones including parathyroid hormone (PTH), parathyroid hormone-related protein (PTHrP), growth hormone (GH), thyroid hormone, and glucocorticoids, and regulates the production of PTHrP and GH.

- Thus through numerous means IGF-I plays a key role in all aspects of skeletal development, the skeleton's subsequent remodeling, and its response to hormonal and environmental factors.

Insulin-like Growth Factor-

Daniel D. Bikle and Yongmei Wa

Veterans Affairs Medical Cente
San Francisco, California, USA

Fig. 1. Working model of IGF-IR/integrin interactions in bone cells.

Disorders of the growth plate

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Warren Alpert Medical School of Brown University,
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593 Eddy Street, Providence, RI 02903, USA
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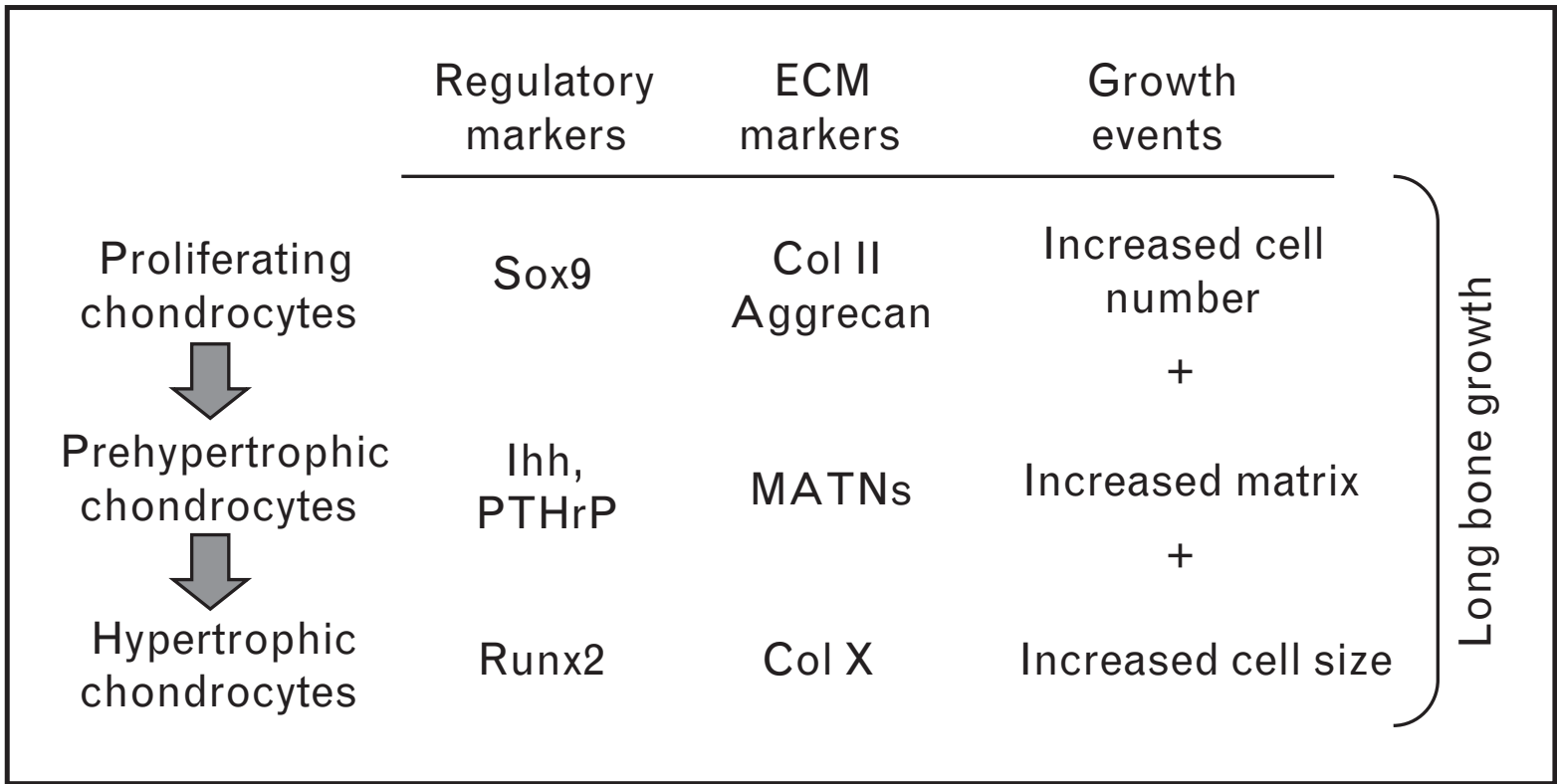e-mail: Chanika_Phornphutkul@brown.edu

Purpose of review
To summarize the recent advances in our understanding of the majors genes involved in
chondrogenesis and their molecular mechanisms.

Recent findings
Disorders of the growth plate and the resulting skeletal dysplasias are a consequence of
defects in genes involved in various stages of the chondrocyte proliferation and
differentiation process. Recent identification of disease genes has provided insights
into the pathophysiology of many skeletal dysplasias.

Summary
This knowledge enhances our understanding of the physiology and pathophysiology of
the growth plate. Many skeletal dysplasias can now be characterized at the molecular
level, allowing clinicians to provide accurate molecular diagnoses and counseling.
Further research in this area will likely provide insights into possible therapeutic options
for disorders of the growth plate.

Figure 1 The organization of the growth plate, showing the stages of chondrogenesis, the matrix constituents and the transcription factors that serve as markers for the stages of chondrocyte differentiation

Col II, collagen II; Col X, collagen X; Ihh, Indian Hedgehog; MATNs, matrilins; PTHrP, parathyroid hormone-related protein.

Disorders of the growth plate

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Figure 2 Examples of genetic defects in key regulators or extracellular matrix during various stages of chondrogenesis resulting in specific skeletal dysplasia

	Regulatory markers	ECM markers	Skeletal dysplasia
Proliferating chondrocytes	Sox9		Campomelic dysp
		Col II	SED
Prehypertrophic chondrocytes	Ihh PTHrP		Brachydactyl type A1 Metaphyseal chondrodysplasia, Jansen type
		MATNs	MED
Hypertrophic chondrocytes	Runx2		CCD
		Col X	Schmid metaphyseal chondrodysplasia

CCD, cleidocranial dysplasia; Col II, collagen II; Col X, collagen X; Ihh, Indian Hedgehog; MATNs, matrilins; MED, multiple epiphyseal dysplasia; PTHrP, parathyroid hormone-related protein; SED, spondyloepiphyseal dysplasia.

Growth plate biology: new insights

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Tel: +1 617 726 2909; e-mail: rmarino1@partners.org

Purpose of review

To discuss the most recent findings of growth plate regulation and physiology. The mechanism of endochondrial bone growth is incompletely understood and continues to be an active area of research.

Recent findings

In this review, new understandings of growth plate chondrocyte regulation of proliferation, differentiation and ossification are discussed. Through genetic studies potential signaling pathways are proposed and new insights into hormonal influences on growth are offered. New potential genetic pathways regulating growth are suggested and finally skeletal dysplasia and potential emerging treatment are considered.

Summary

The findings discussed here continue to build the understanding of the mechanisms of growth. As our knowledge increases potential treatments for growth inhibiting conditions can be developed.

Table 1 Summary of factors involved in growth plate maturation

Factor	Source	Actions
Ihh	Prehypertrophic chondrocytes, hypertrophic chondrocytes	Stimulates PTHrP, regulates resting zone to proliferative zone chondrocytes, stimulates proliferative chondrocytes to proliferate, determines distance at the end of the bone when proliferating chondrocytes differentiate into hypertrophic chondrocytes
PTHrP	Perichondrial chondrocytes	Maintains proliferative chondrocytes in the proliferative pool
Cyclin D1	Proliferative chondrocytes	Transitions cells from G1 to S phase
Runx2	Proliferative chondrocytes	Promotes chondrocyte differentiation
Runx3	Proliferative chondrocytes	Promotes chondrocyte differentiation
CSPG	Throughout growth plate	Binds Ihh influencing its distribution throughout the growth plate
dEF1	Throughout growth plate	Negative regulator of Ihh
ADAMTS-12	Proliferating and prehypertrophic chondrocytes	Increases PTHrP
ADAMTS-7	Proliferating and prehypertrophic chondrocytes	Increases PTHrP and negatively modulates chondrocyte differentiation
TGF-β	Perichondrium	Promotes differentiation and matrix synthesis
BMPs	Perichondrium, hypertrophic and proliferative chondrocytes	Increases Ihh production and chondrocyte differentiation
C/EBPβ	Late proliferative and prehypertrophic chondrocytes	Promotes chondrocyte differentiation from proliferative to hypertrophic
Panexxin3	Prehypertrophic chondrocytes	Promotes transition of proliferative to hypertrophic chondrocytes
Capn4	Hypertrophic chondrocytes	Modulates terminal cell differentiation
SDF-1	Bone marrow area adjacent to the hypertrophic cartilage	Enhances chondrocyte hypertrophy
SOX9	Chondroprogenitor cells, resting and proliferative chondrocytes	Responsible for proliferation and differentiation of the fetal growth plate, negative regulator of vascularization, cartilage resorption and trabecular bone formation
FGFs	Proliferative, prehypertrophic and hypertrophic chondrocytes	Inhibit proliferation

Growth plate biology: new insights
Rose Marino

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Summary
The findings discussed here continue to build the understanding of the mechanisms of growth. As our knowledge increases potential treatments for growth inhibiting conditions can be developed.

In conclusion endochondral bone growth is controlled by a complicated system of intracrine, paracrine and endocrine factors. The physiology and pathophysiology of the growth plate remains a dynamic area of research. As the understanding of this field grows so will novel therapeutic strategies for growth disorders such as the skeletal dysplasias.

REVIEW ARTICLE

Ego Seeman

Bone quality: the material and structural basis of bone strength
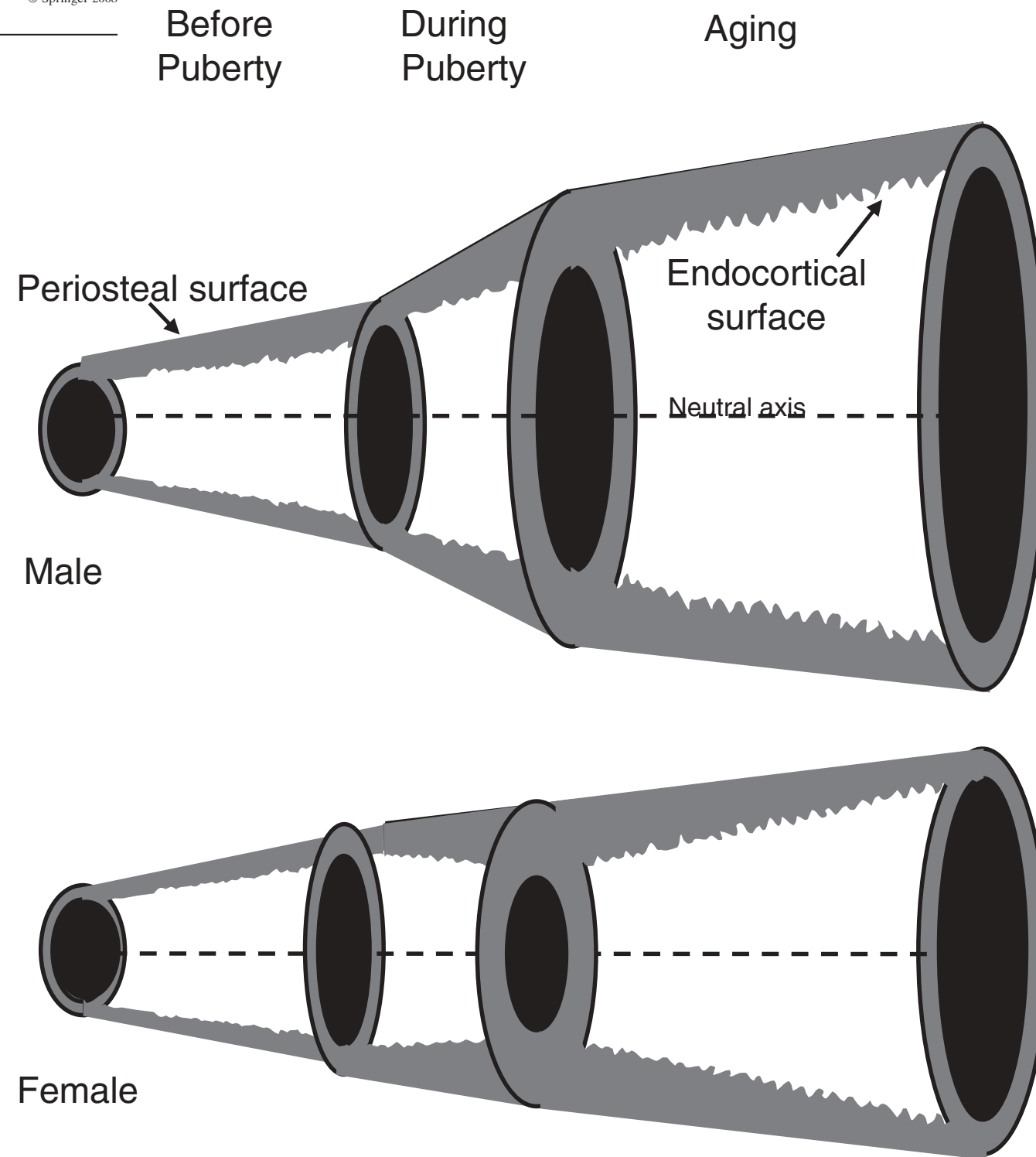
Fig. 2. Sex differences in periosteal apposition and endocortical resorption in tubular bones. Before puberty, there is little sex difference in the bone diameters and bone mass. During puberty, periosteal apposition continues in the male, thickening the cortex, while little change occurs in endocortical resorption
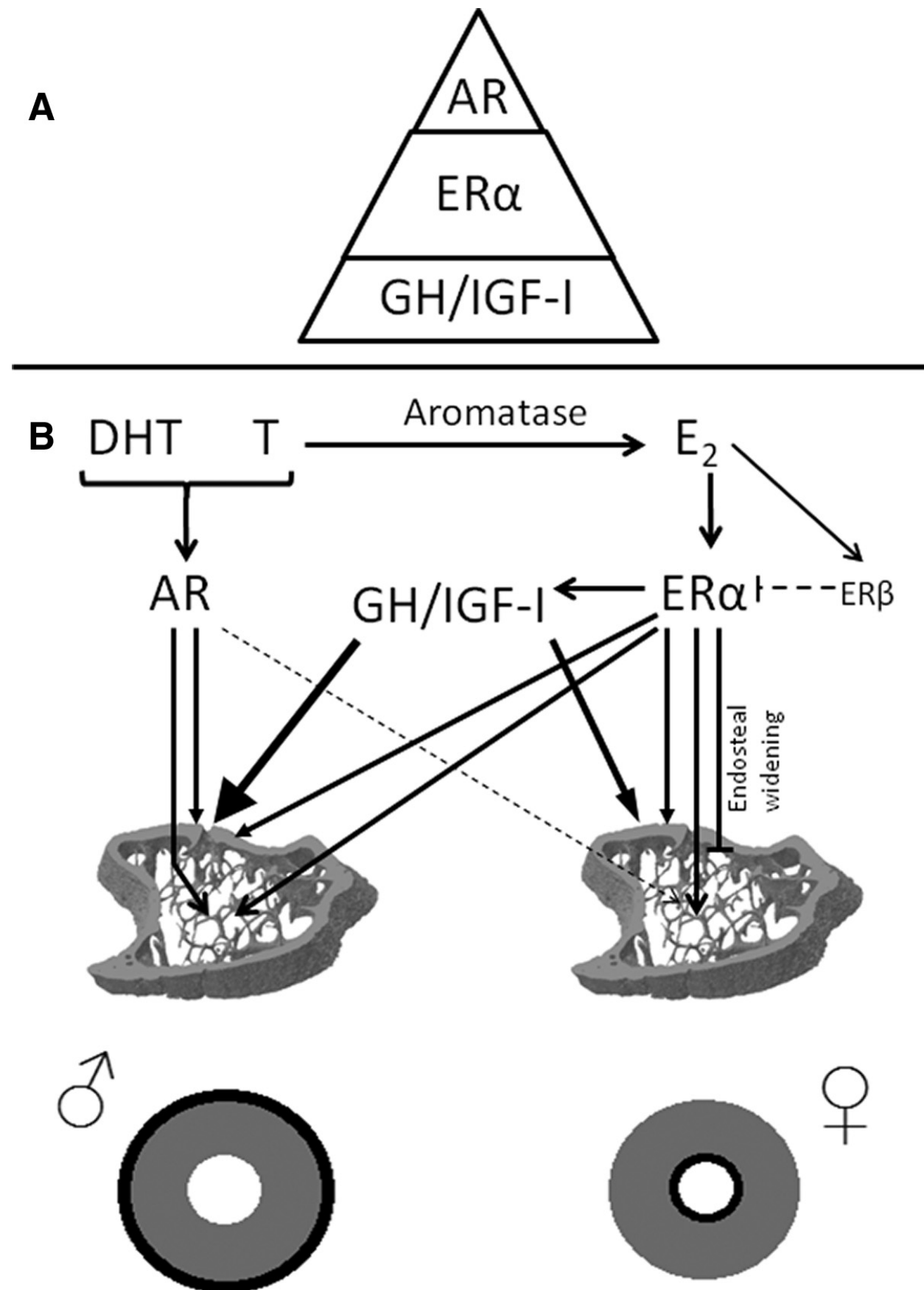
Sex steroid actions in male bone

Dirk VANDERSCHUEREN*, Michaël R. LAURENT*, Frank CLAESSENS, Evelien GIELEN, Marie K. LAGERQUIST, Liesbeth VANDENPUT, Anna E. BÖRJESSON †, and Claes OHLSSON †

Clinical and Experimental Endocrinology (D.V.) and Gerontology and Geriatrics (M.R.L., E.G.), Department of Clinical and Experimental Medicine; Laboratory of Molecular Endocrinology, Department of Cellular and Molecular Medicine (M.R.L., F.C.); and Centre for Metabolic Bone Diseases (D.V., M.R.L., E.G.), KU Leuven, B-3000 Leuven, Belgium; and Center for Bone and Arthritis Research, Department of Internal Medicine and Clinical Nutrition, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, 413 45 Gothenburg, Sweden. (M.K.L., L.V., A.E.B., C.O.)

Figure 4.

Schematic representation of the effects of sex steroids and their receptors in the development of male and female pubertal bone development. A, Pyramid hierarchy of sexual dimorphism in bone: Given the severely disordered bone development in case reports of ERα mutations or aromatase deficiency, compared to the normal female-like bone structure in XY females with androgen insensitivity syndrome (AIS), the effects of ERα should be considered critical, whereas AR provides further benefits which however are unable to compensate for severely decreased ERα activation. Even more severe is the skeletal phenotype of developmental disruption of the GH/IGF-I-axis in both genders, and skeletal sexual dimorphism is completely lacking in GH-receptorknock-out mice (with very low circulating IGF-I levels) (78). B, Androgens like T can be converted via aromatization to estrogens and can thus activate both AR and ERα. In males, both AR and ERα stimulate cortical and trabecular bone development. During puberty, males have greater periosteal expansion than females (black outer circle, figure bottom), which depends both on AR (in late puberty) and ERα (in early puberty) but especially on IGF-I (probably via central aromatization of androgens) (78, 82). Trabecular bone formation is increased by ERα in males (220), whereas both ERα and AR can inhibit trabecular bone resorption. Additionally, AR inactivation has been shown to slow mineralization in early growth, when bone turnover is high (170). In females, ERα is responsible for both trabecular and cortical bone mass accretion, but their cortical thickness relies more on limiting endocortical expansion (black inner circle, figure bottom). ERα inhibits endosteal bone resorption and stimulates periosteal bone formation (179), although the latter is lower compared to males (82). Females have higher endosteal bone formation (78) due to actions of ERα (95). Estrogens also stimulate trabecular bone formation in female mice (219, 221, 222). Both androgens and estrogens can decrease trabecular bone

2014 VANDERSCHUEREN Male Bone

Sex steroid actions in male bone

Dirk VANDERSCHUEREN*, Michaël R. LAURENT*, Frank CLAESSENS, Evelien GIELEN,
Marie K. LAGERQUIST, Liesbeth VANDENPUT, Anna E. BÖRJESSON †, and
Claes OHLSSON †

Clinical and Experimental Endocrinology (D.V.) and Gerontology and Geriatrics (M.R.L., E.G.), Department of Clinical and Experimental Medicine; Laboratory of Molecular Endocrinology, Department of Cellular and Molecular Medicine (M.R.L., F.C.); and Centre for Metabolic Bone Diseases (D.V., M.R.L., E.G.), KU Leuven, B-3000 Leuven, Belgium; and Center for Bone and Arthritis Research, Department of Internal Medicine and Clinical Nutrition, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, 413 45 Gothenburg, Sweden. (M.K.L., L.V., A.E.B., C.O.)
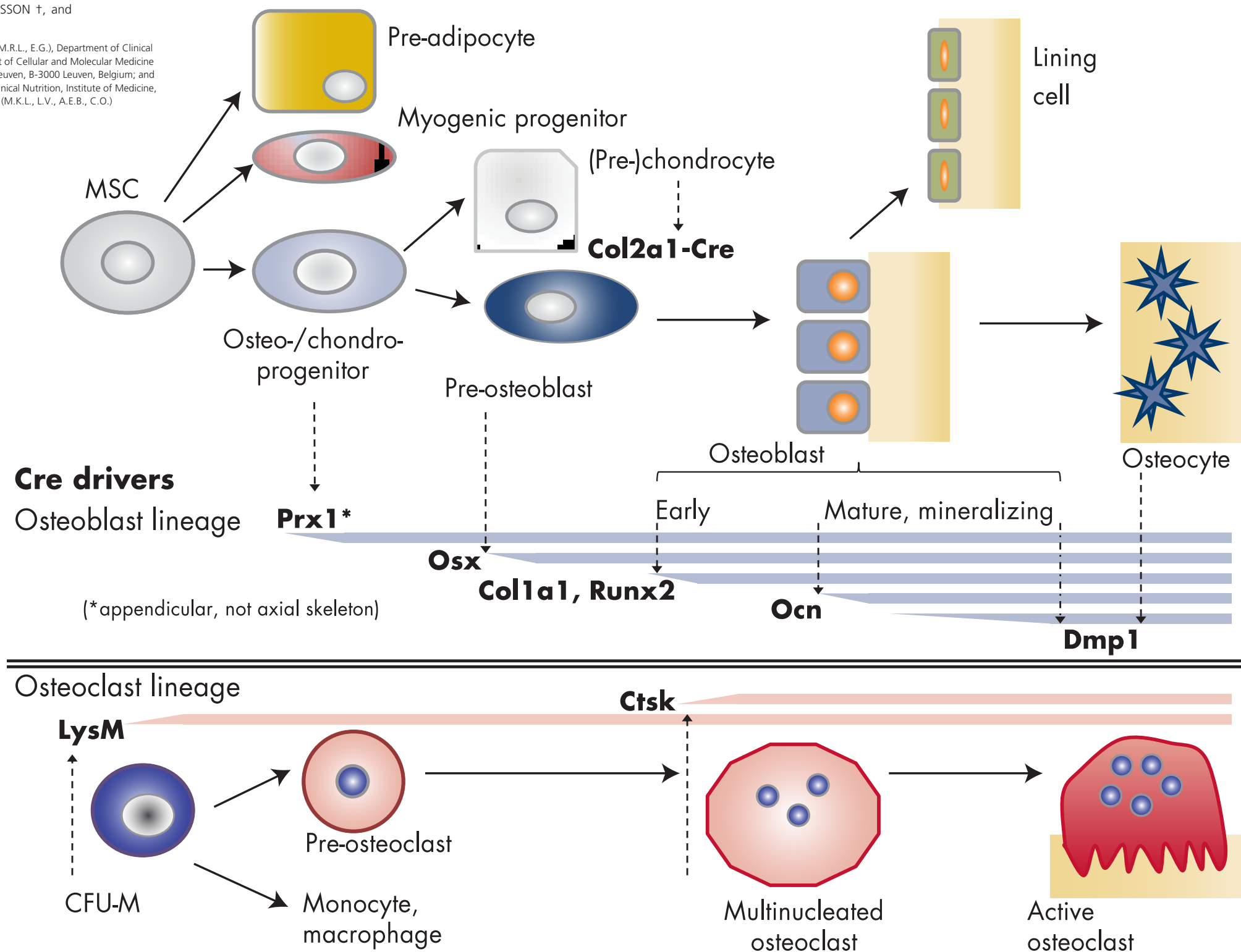
Figure 1. Overview of Cre promoter mouse strains (in bold) that have been crossed with floxed-ERα/ERβ- or AR-transgenic mice to generate conditional knockout models discussed in Section V. Osteoblast and osteoclast differentiation are schematically represented above and below, respectively, and the maturation stage at which the respective promoters become active is indicated by the blue and red horizontal bars, respectively. Note that Cre-mediated target gene excision occurring at a specified maturation stage also affects all downstream differentiation stages. Col2a1, collagen, type II, α1; Prx1, paired related homeobox 1; Osx, osterix (transcription factor Sp7); Col1a1, collagen, type I, α1; MSC, mesenchymal stem cell; CFU-M, colony-forming unit-monocyte.

2014 VANDERSCHUEREN Male Bone

M. Michael Cohen Jr.*
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TABLE XX. Types of Collagen in Bone and Cartilage

Bone
    Major collagen   Type I
                                Fibrillar collagen
    Minor collagen   Type XI
                                Fibrillar collagen; regulates collagen fibril diameter and associates proteoglycans with collagen fibrillar network

Cartilage
    Major collagen   Type II
                                Fibrillar collagen
    Minor collagen   Type IX
                                Fibril-associated collagen; localized to surface of type II fibrils
                                Type X
                                Network collagen; expressed in hypertrophic cartilage
                                Type XI
                                Fibrillar collagen; regulates collagen fibril diameter and associates proteoglycans with collagen fibrillar network

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TABLE XXI. Collagenopathies

Type of collagenopathy	Chromosome location	Gene
Type I collagenopathies		
Osteogenesis imperfecta I (normal teeth)	17q21-q22	*COL1A1*
Osteogenesis imperfecta I (normal teeth)	7q22.1	*COL1A2*
Osteogenesis imperfecta I (dentinogenesis imperfecta)	17q21-q22	*COL1A1*
Osteogenesis imperfecta I (dentinogenesis imperfecta)	7q22.1	*COL1A2*
Osteogenesis imperfecta II	17q21-q22	*COL1A1*
Osteogenesis imperfecta II	7q22.1	*COL1A2*
Osteogenesis imperfecta III	17q21-q22	*COL1A1*
Osteogenesis imperfecta III	7q22.1	*COL1A2*
Osteogenesis imperfecta IV (normal teeth)	17q21-q22	*COL1A1*
Osteogenesis imperfecta IV (normal teeth)	7q22.1	*COL1A2*
Osteogenesis imperfecta IV (dentinogenesis imperfecta)	17q21-q22	*COL1A1*
Osteogenesis imperfecta IV (dentinogenesis imperfecta)	7q22.1	*COL1A2*
Type II collagenopathies		
Achondrogenesis II (Langer—Saldino)	12q13.1-q13.3	*COL2A1*
Hypochondrogenesis	12q13.1-q13.3	*COL2A1*
Spondyloepiphyseal dysplasia congenita	12q13.1-q13.3	*COL2A1*
Spondyloepimetaphyseal dysplasia (Strudwick)	12q13.1-q13.3	*COL2A1*
Kniest dysplasia	12q13.1-q13.3	*COL2A1*
Spondyloepiphyseal dysplasia (brachydactyly)	12q13.1-q13.3	*COL2A1*
Mild spondyloepiphyseal dysplasia (premature onset arthrosis)	12q13.1-q13.3	*COL2A1*
Stickler dysplasia (type I)	12q13.1-q13.3	*COL2A1*
Type IX collagenopathies		
Multiple epiphyseal dysplasia (Fairbanks and Ribbing types)	6q13	*COL9A1*
Multiple epiphyseal dysplasia (Fairbanks and Ribbing types)	1p32.2-p33	*COL9A2*
Multiple epiphyseal dysplasia (Fairbanks and Ribbing types)	20q13.3	*COL9A3*
Type X collagenopathy		
Metaphyseal dysplasia (Schmid)	6q21-q22.3	*COL10A1*
Type XI collagenopathies		
Stickler dysplasia (type II)	1p21	*COL11A1*
Marshall syndrome	6p21.3	*COL11A2*
Otospondylomegaepiphyseal dysplasia (OSMED), AR	6p21.3	*COL11A2*
Otospondylomegaepiphyseal dysplasia (OSMED), AD	6p21.3	*COL11A2*

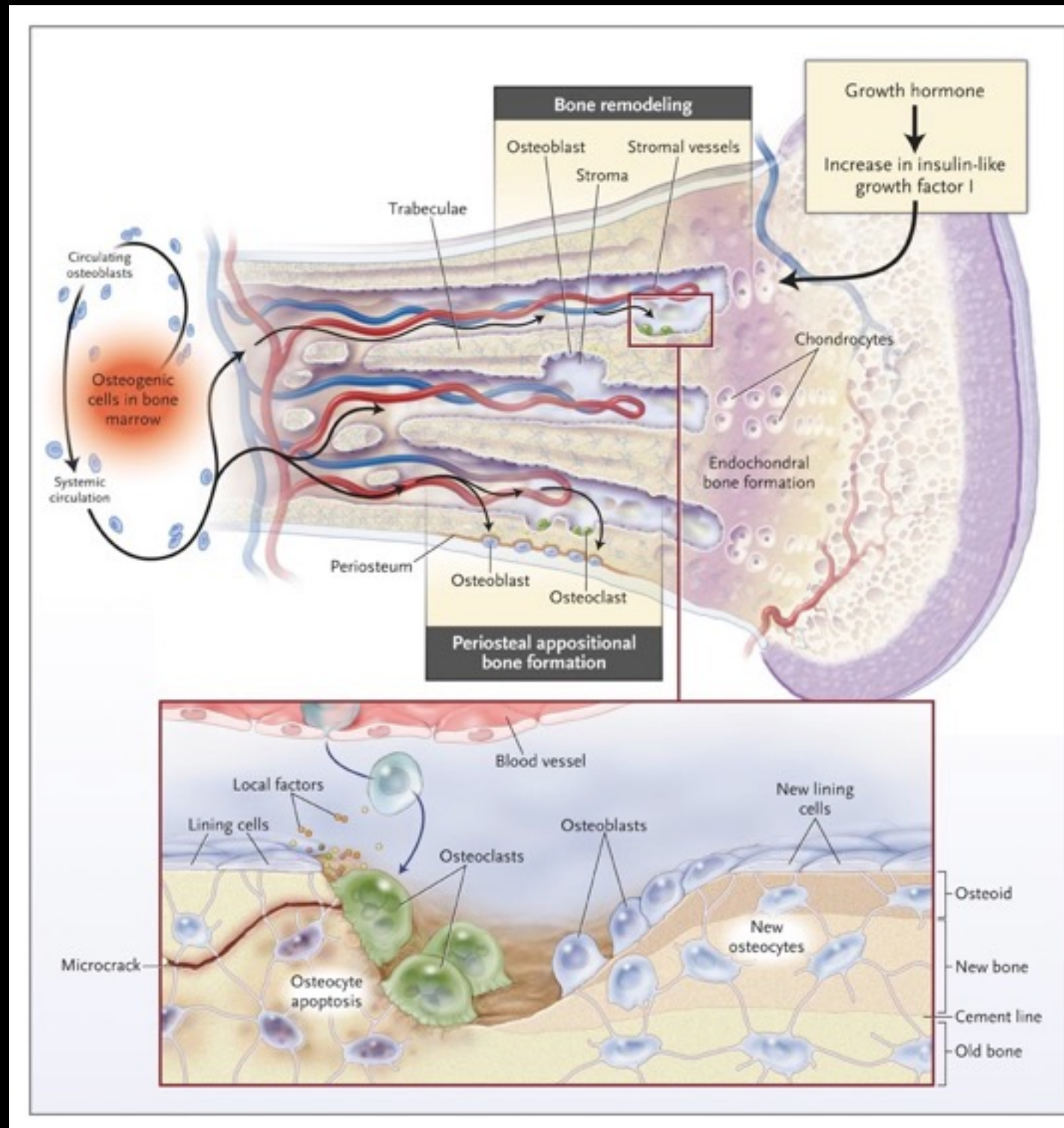Data based on International Nosology and Classification of Constitutional Disorders of Bone [2003].
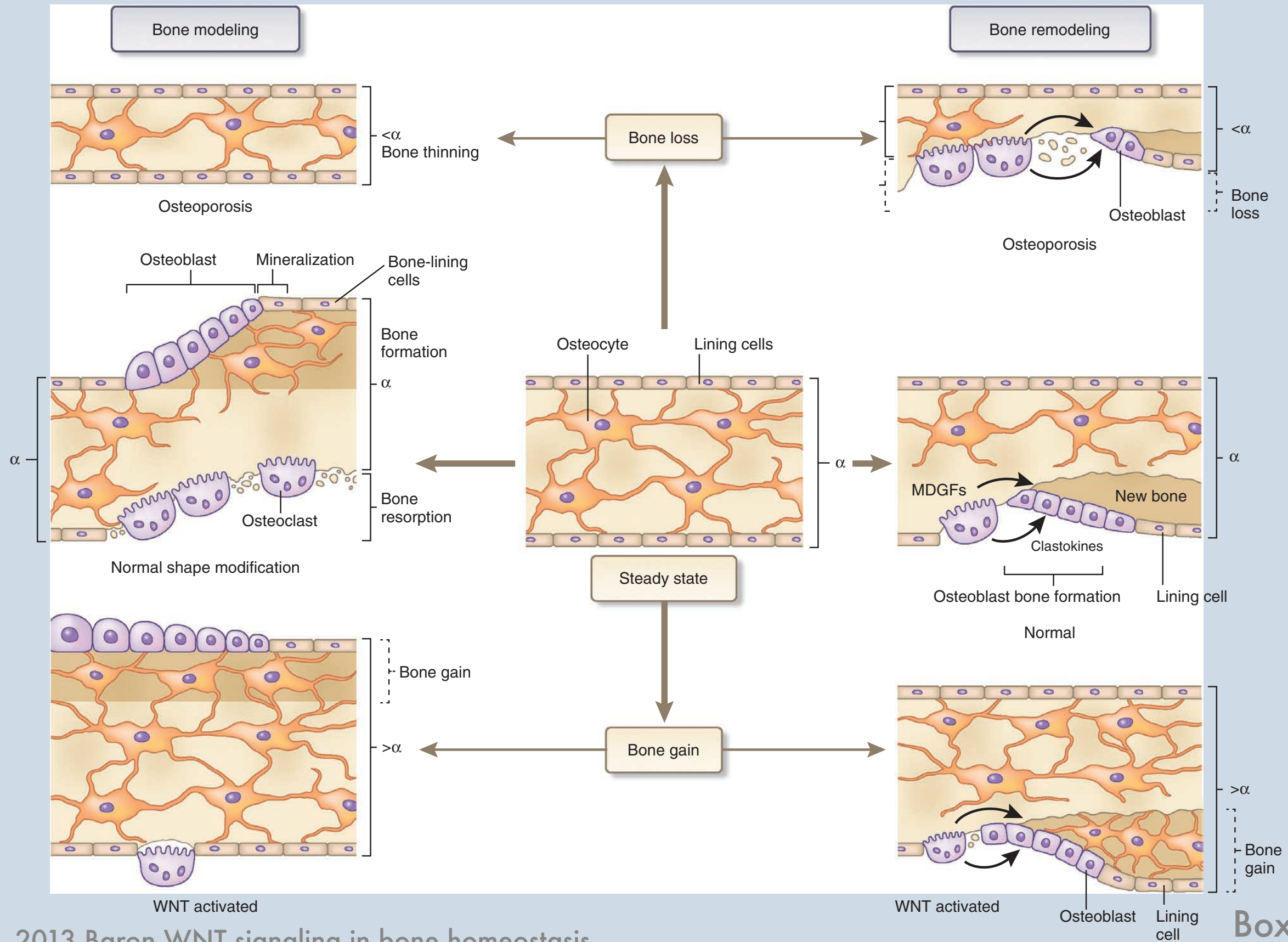
Controllo della massa ossea

Bone Mass Lifecycle
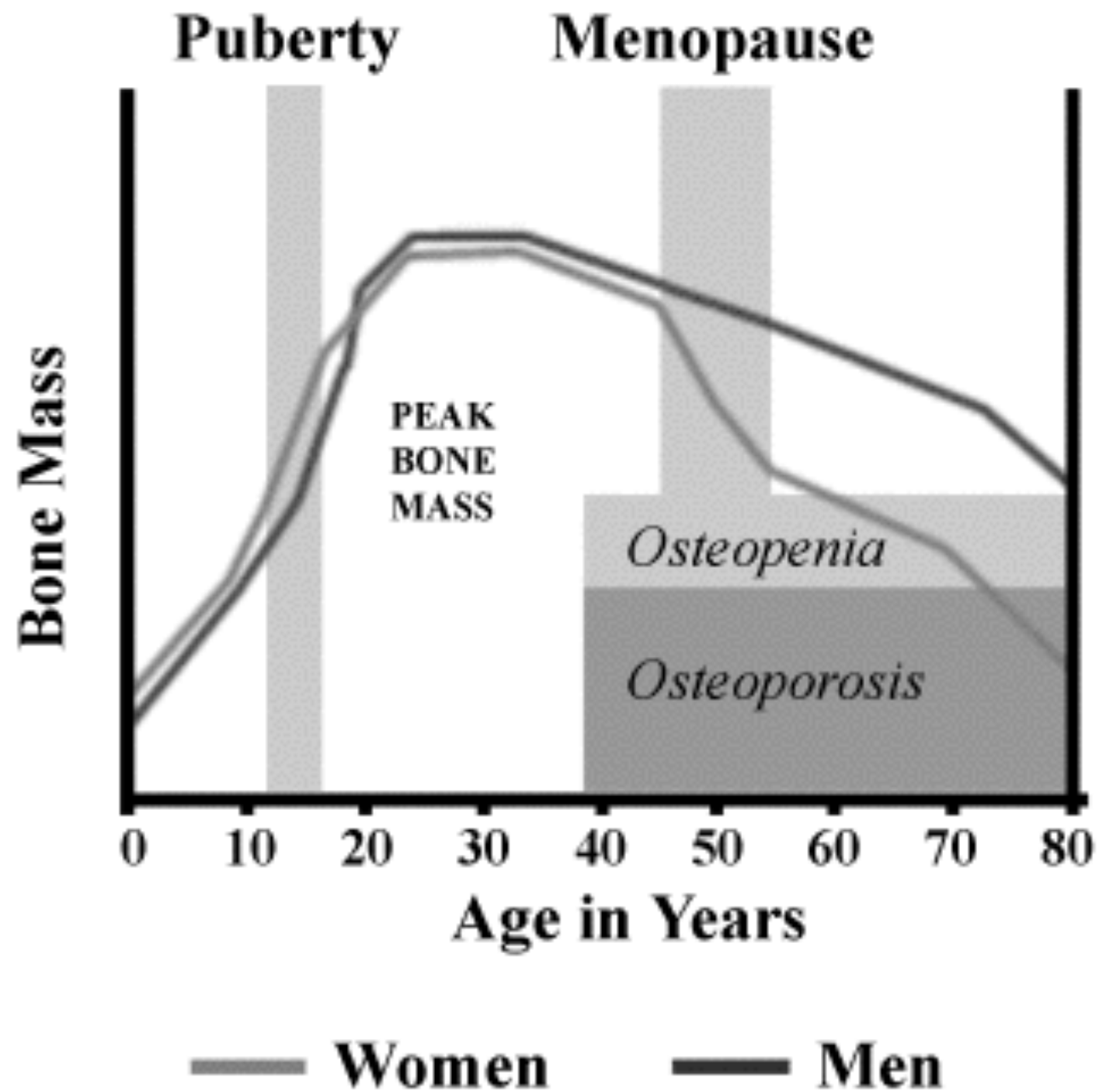
Bone Remodeling in Basic Multicellular Units and Bone Modeling by Osteoblasts and Osteoclasts
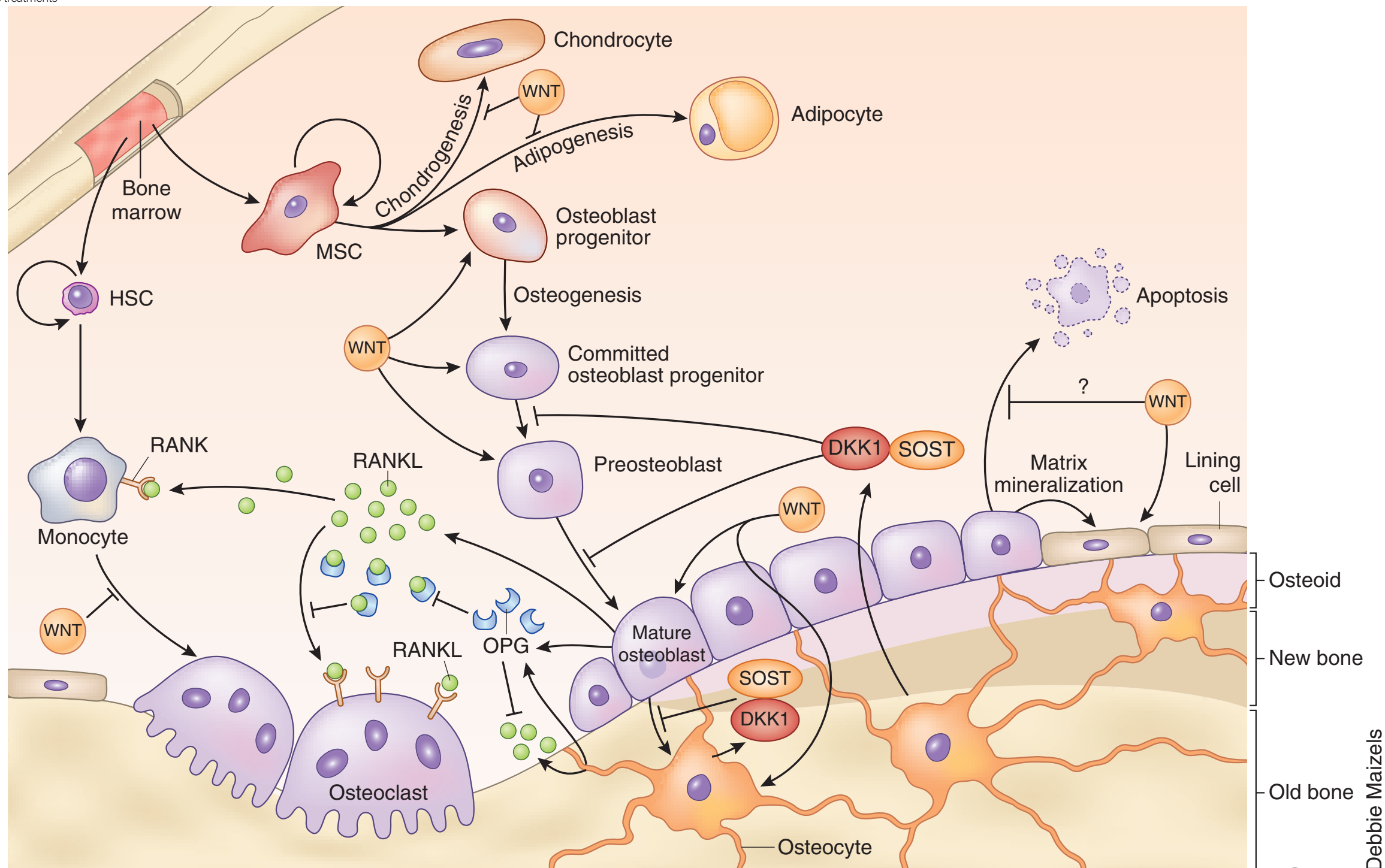
Bone modeling and remodeling

Bone modeling

Osteoporosis

Bone thinning <α

Osteoblast — Mineralization — Bone-lining cells

Bone formation α

Osteoclast

Bone resorption

α

Normal shape modification

Bone gain

>α

WNT activated

Bone remodeling

Bone loss

Osteoblast

Osteoporosis

<α

Bone loss

Osteocyte — Lining cells

Steady state

α

MDGFs

New bone

Clastokines

Osteoblast bone formation — Lining cell

Normal

α

Bone gain

WNT activated

Osteoblast — Lining cell

>α

Bone gain

Impact of WNT/b-catenin signaling on bone cells.

2013 Baron WNT signaling in bone homeostasis

Figure 3

WNT signaling translates mechanosignals in osteocytes

Figure 4 Crosstalk of WNT, PTH and BMP signaling between bone cells. Osteocytes control bone formation through the secretion of the WNT antagonists sclerostin (SOST) and DKK1, the expression of which is regulated by mechanosignals and signaling of PTH and BMP. PTH represses, whereas BMPR1A-mediated BMP signaling induces, expression of these antagonists. Moreover, WNT signaling in osteocytes controls the production of OPG, which is the decoy receptor for the key osteoclast differentiation factor RANKL. Osteoblast-expressed WNT5a stimulates differentiation of osteoclast precursors as a result of binding to the FZD–ROR2 receptor complex. In a feedback loop for bone remodeling, osteoclasts stimulate the local differentiation of osteoblasts at the end of the resorption phase by secreting WNT ligands. In addition, activation of PTH1R-mediated signaling in osteoblasts and osteocytes leads to β-catenin stabilization and, thus, activation of WNT signaling.
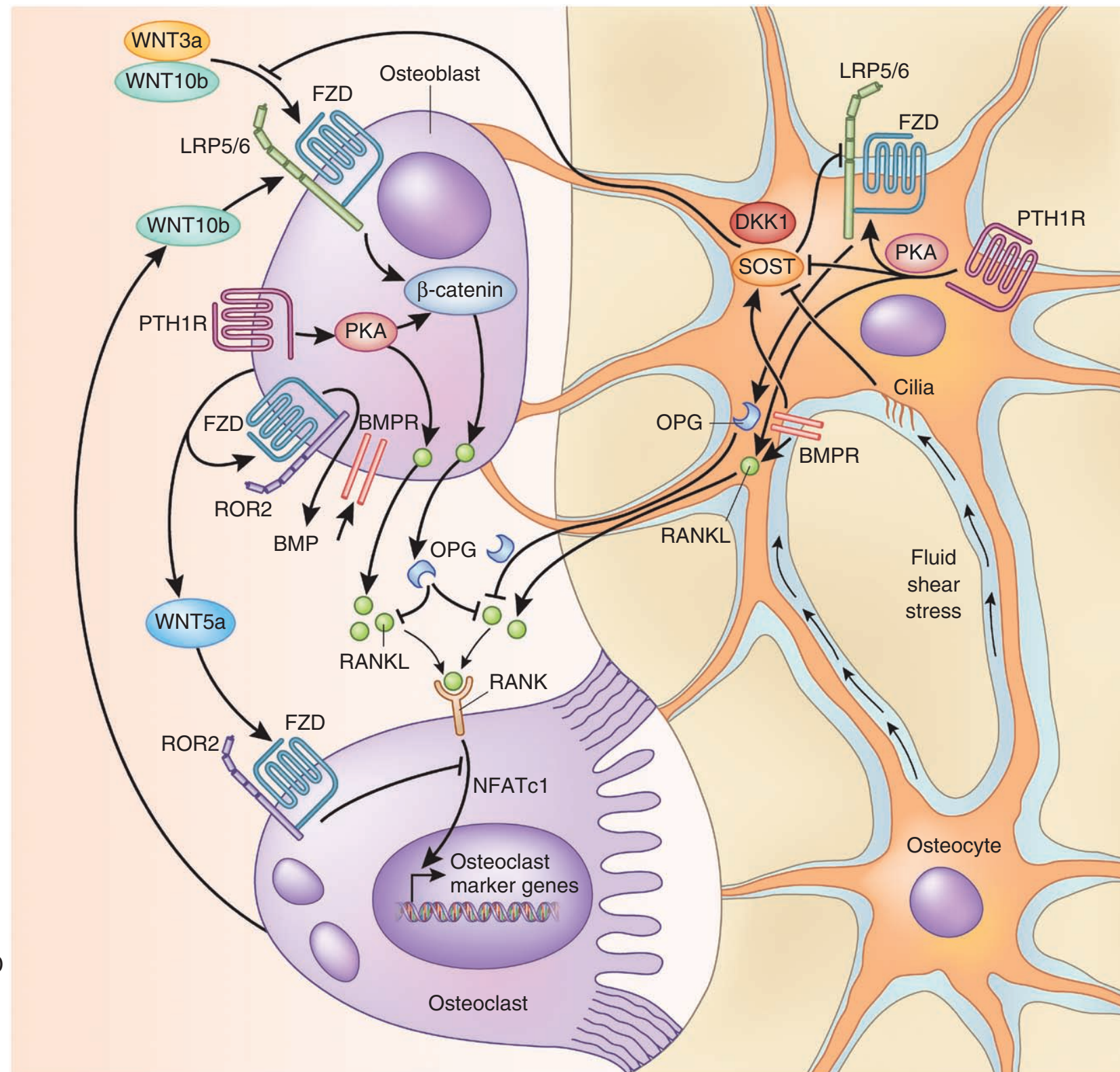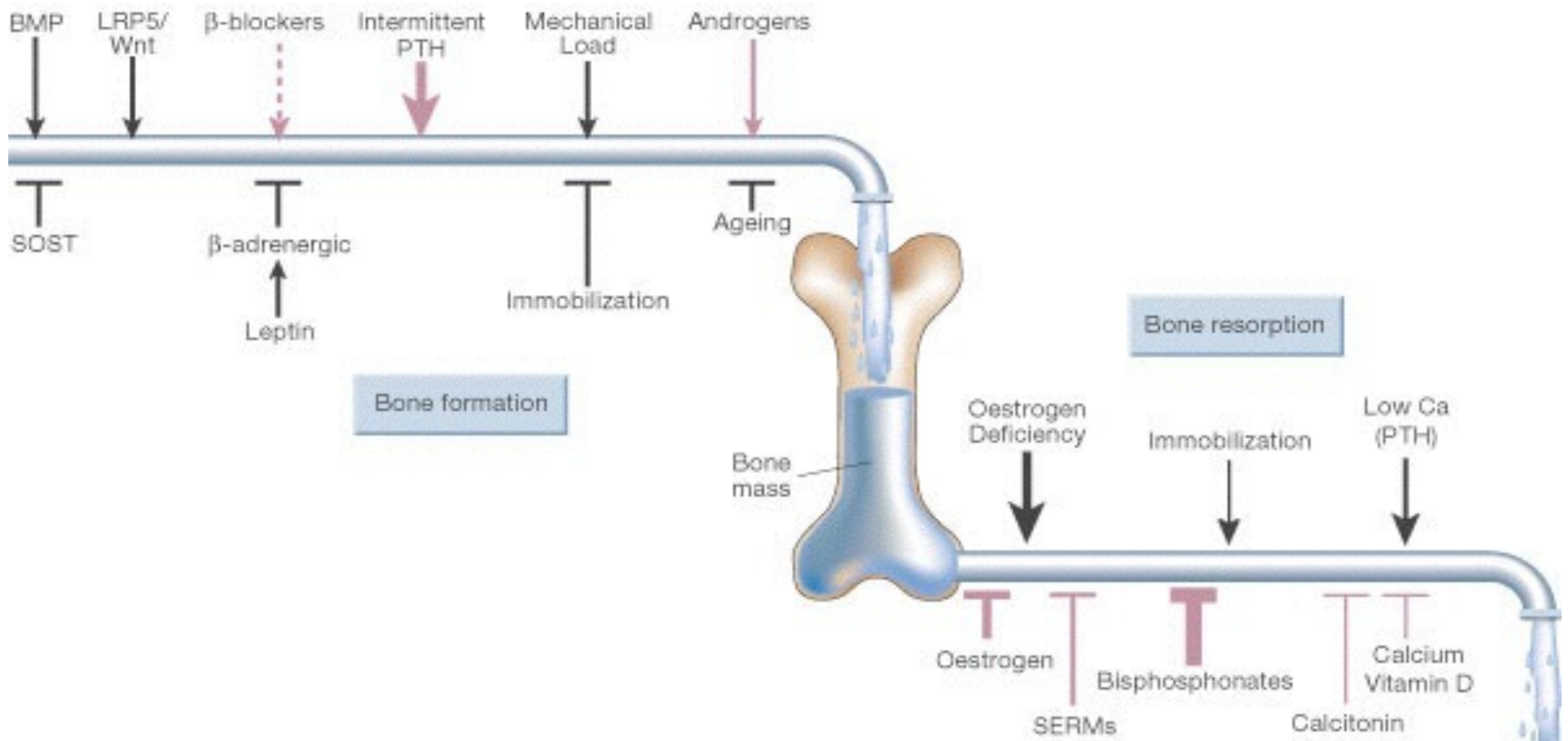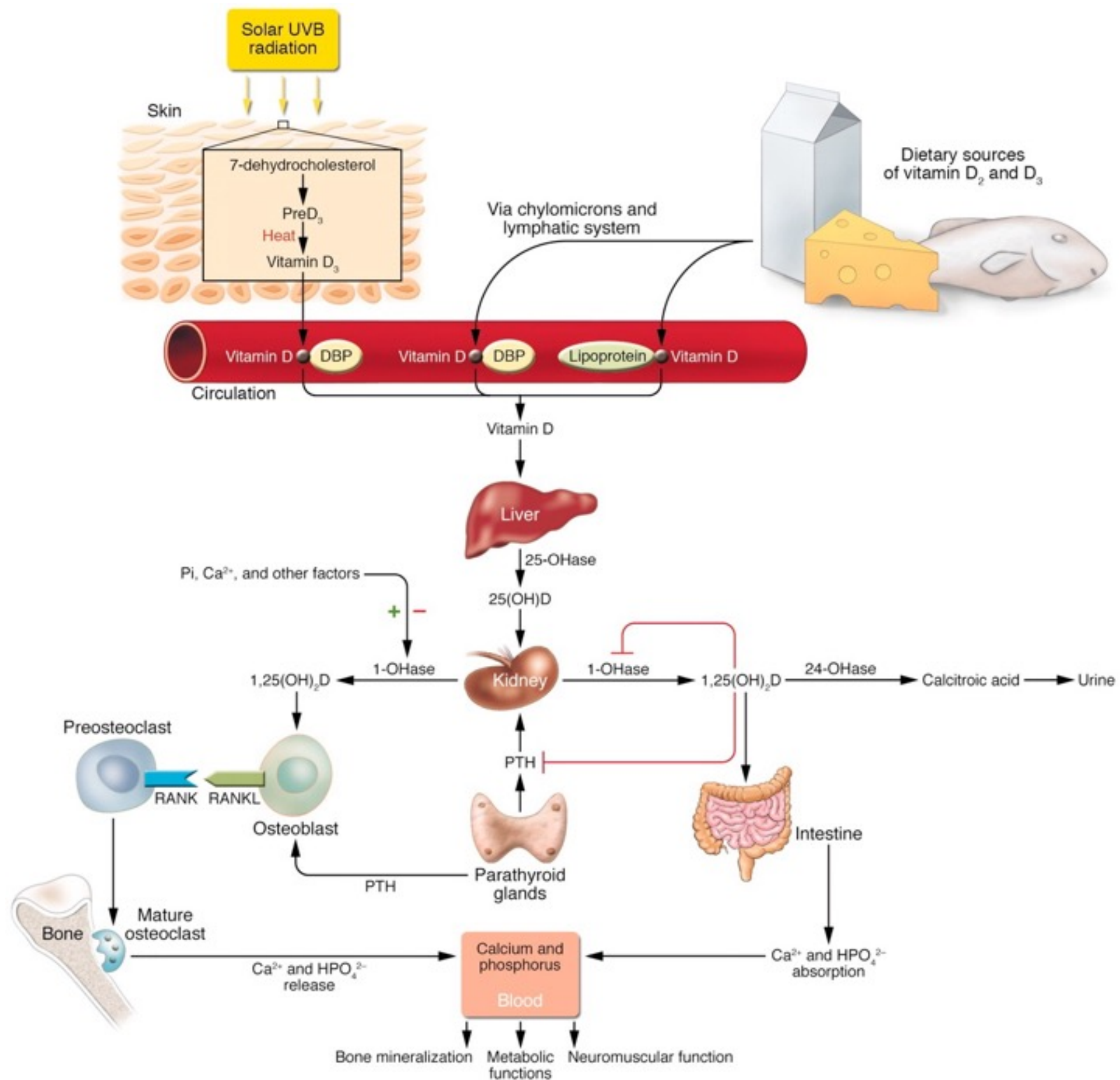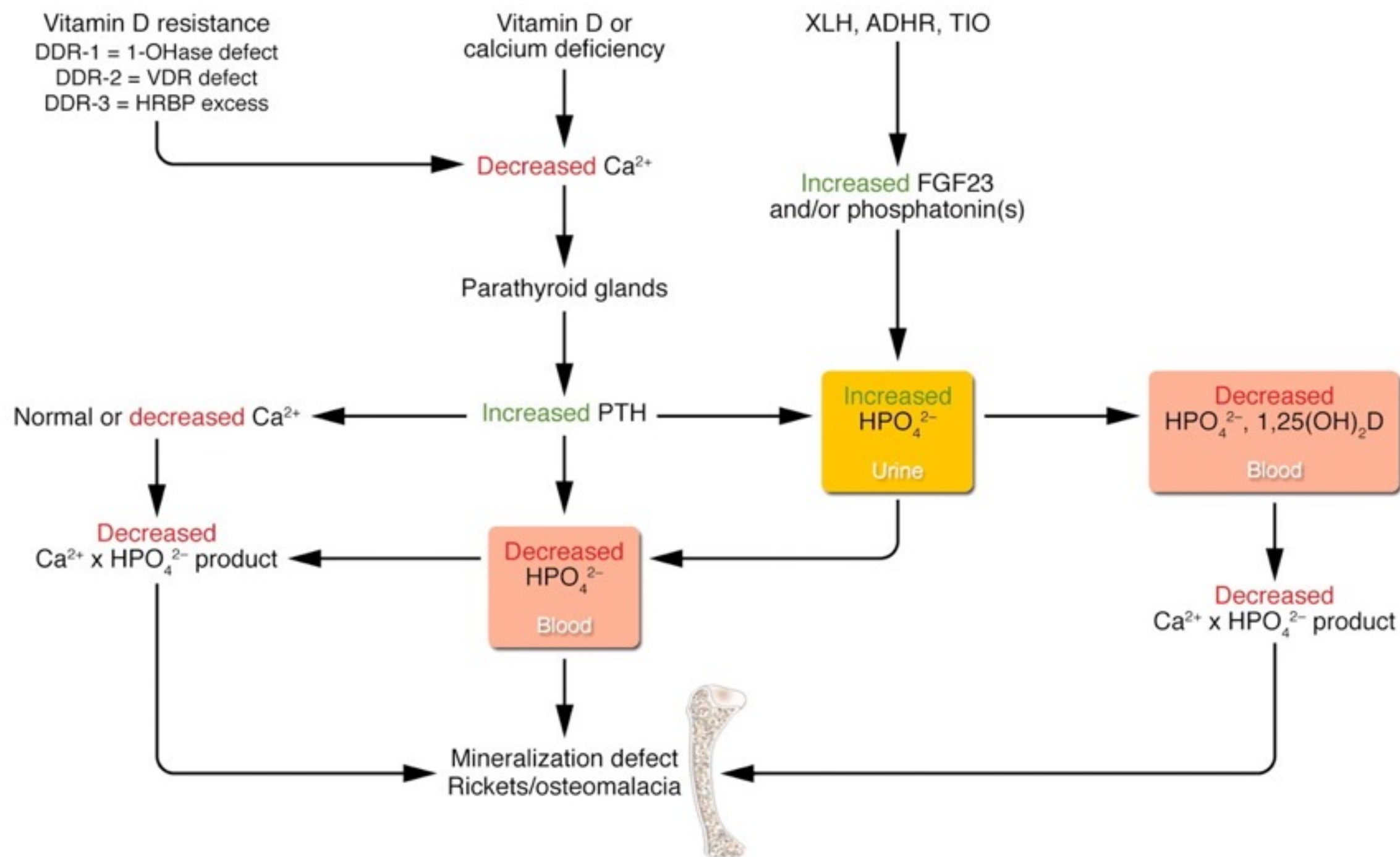
Shun-ichi Harada & Gideon A. Rodan, Nature 423:349-355, 2003

Solar UVB radiation

Skin

7-dehydrocholesterol

PreD₃
Heat
Vitamin D₃

Via chylomicrons and lymphatic system

Dietary sources of vitamin D₂ and D₃

Vitamin D • DBP   Vitamin D • DBP   Lipoprotein • Vitamin D

Circulation

Vitamin D

Liver

25-OHase

25(OH)D

Pi, Ca²⁺, and other factors

+ −

1,25(OH)₂D   1-OHase   Kidney   1-OHase   1,25(OH)₂D   24-OHase   Calcitroic acid   Urine

Preosteoclast

RANK RANKL

Osteoblast

PTH

Intestine

Bone

Mature osteoclast

PTH   Parathyroid glands

Ca²⁺ and HPO₄²⁻ release

Calcium and phosphorus

Blood

Ca²⁺ and HPO₄²⁻ absorption

Bone mineralization   Metabolic functions   Neuromuscular function

Holick, M. F. J. Clin. Invest. 2006;116:2062-2072

JCI

Vitamin D resistance
DDR-1 = 1-OHase defect
DDR-2 = VDR defect
DDR-3 = HRBP excess

Vitamin D or
calcium deficiency

XLH, ADHR, TIO

Decreased Ca^{2+}

Increased FGF23
and/or phosphatonin(s)

Parathyroid glands

Normal or decreased Ca^{2+}

Increased PTH

Increased HPO_4^{2-}
Urine

Decreased HPO_4^{2-}, $1,25(OH)_2D$
Blood

Decreased Ca^{2+} x HPO_4^{2-} product

Decreased HPO_4^{2-}
Blood

Decreased Ca^{2+} x HPO_4^{2-} product

Mineralization defect
Rickets/osteomalacia

Holick, M. F. J. Clin. Invest. 2006;116:2062-2072

Gli esami di laboratorio

Situazioni

Neonato:

- ipocalcemia neonatale

- ipercalcemia neonatale

- prematuro

Lattante - Bambino:

- fratture ripetute

- osteoporosi

- rachitismo

- osteogenesi imperfetta

- terapie croniche

Il laboratorio "normale"

Lo studio del metabolismo Ca/P si avvale di alcuni esami di base abbastanza semplici:

Calcio, Fosfato, ALP totale, 25 OH Vitamina D e PTH nel sangue

Calcio (rapporto Calcio/creatinina) e Fosfato nelle urine.

Segni biochimici delle principali forme di rachitismo

Patologia	Calcio	Fosfato	ALP	PTH	25-OH-D	$1,25(OH)_2D$
Rachitismo carenziale	N o ↓	N o ↓	↑	↑	N o ↓	N o ↓ o ↑
R da malassorbimento intestinale cr	N o ↓	N o ↓	↑	↑	N o ↓	N o ↓ o ↑
R nelle malattie epato-biliari	N o ↓	N o ↓	↑	↑	N o ↓	↓
R da anticonvulsivanti	N o ↓	N o ↓	↑	↑	↓	N o ↓
R ipofosfatemico familiare	N	↓	↑	N	N	N o ↓*
R vitamina D-dipendente tipo I	↓	↓	↑	↑	N o ↑	↓
R vitamina D-dipendente tipo II	↓	↓	↑	↑	N o ↑	↑

* normali in termini numerici ma inappropriatamente ridotti rispetto all'ipofosfatemia

3 stadi evolutivi di Fraser

Stadio 1

rachitismo precoce con segni Rx e clinici discreti

Ca diminuito, P normale o poco diminuito, ALP e PTH in progressivo aumento

Stadio 2

segni clinici e Rx netti

Ca normale (iperPTH secondario), P diminuito, PTH alto

Stadio 3

demineralizzazione importante, con deficitaria risposta ossea e renale al PTH, persistendo la carenza vitaminica

Ca diminuito, ALP e PTH molto elevate, 25OH-D molto diminuito, 1-25OH$_2$-D variabile

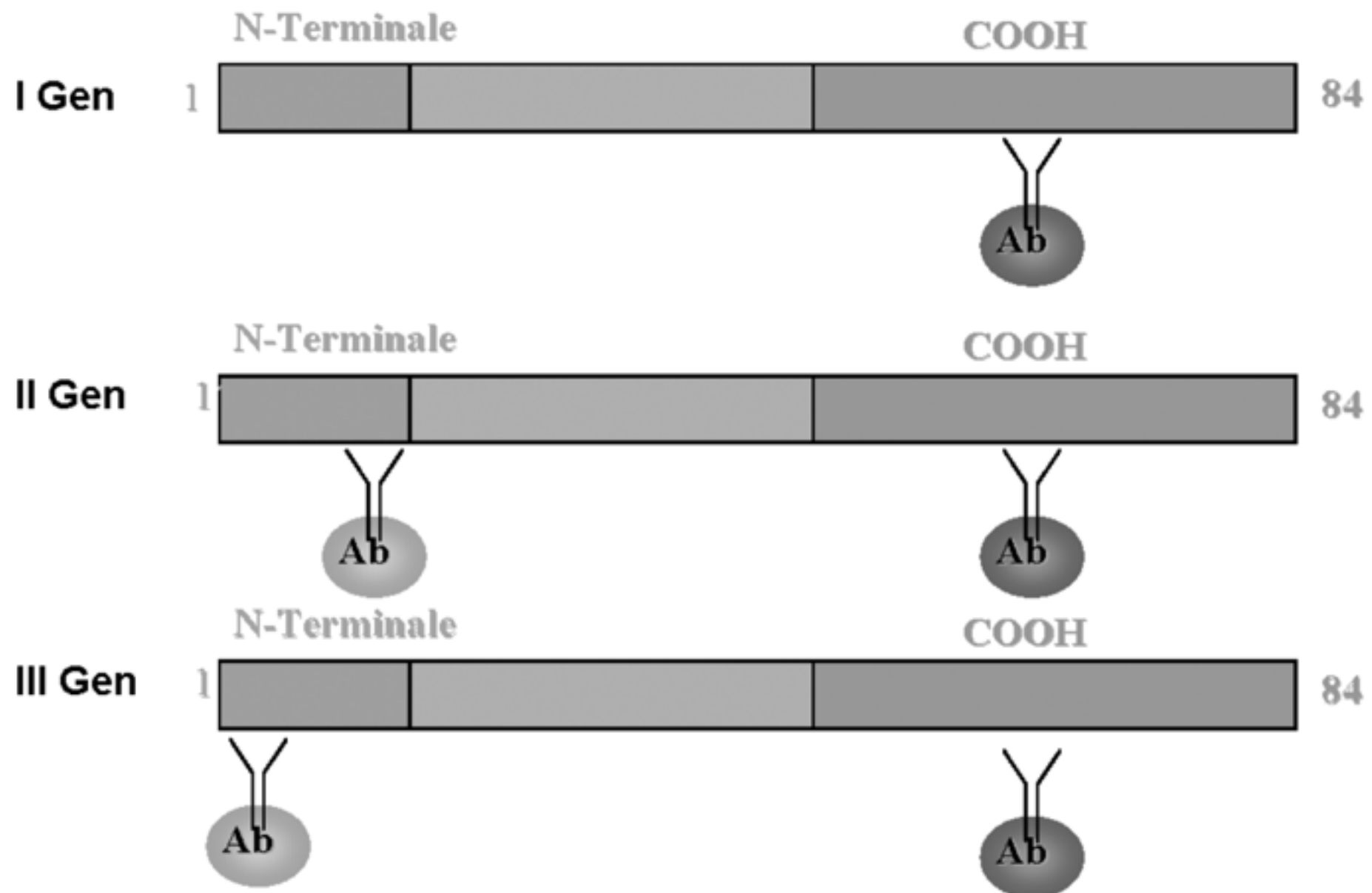Iperaminoaciduria globale, glicosuria a volte, idrossiprolinuria aumentata

Acidosi ipercloremica

Stadi evolutivi di Fraser
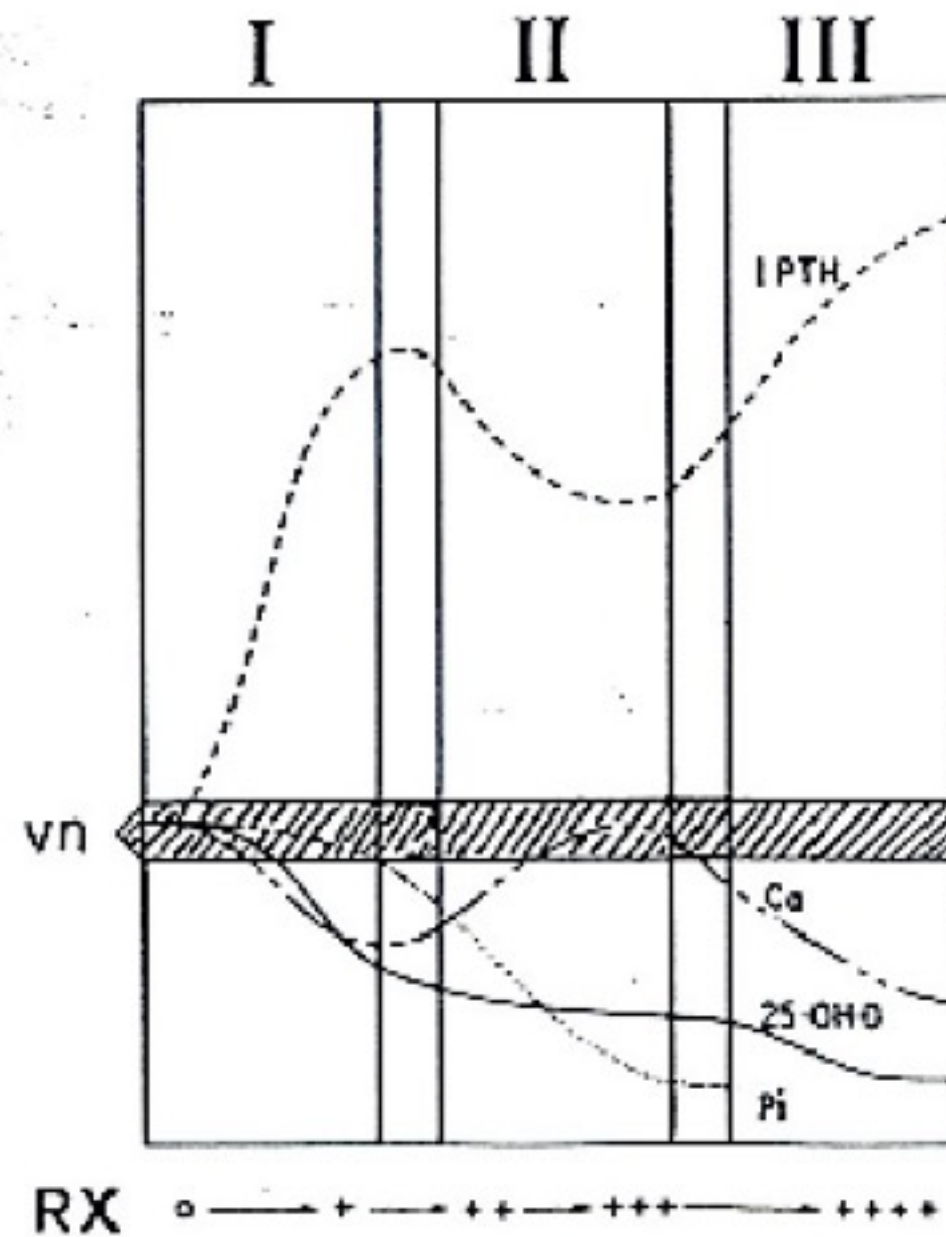
Stadi di progressione del rachitismo secondo Fraser [41].

PTH

PTH

Assay	PTH (ng/l)	PTH (ng/l)	PTH (ng/l)	Median bias (%)
Allegro *intact* PTH	150	300	1000	0
N-tact PTH IRMA	83	160	517	-114,9 (-68,0; -26,2)
PTH IRMA Immunotech	188	369	1216	23,9 (-6,1; -108,3)
ELISA-PTH	149	290	948	-1,6 (-24,3; 47,2)
Total *intact* PTH IRMA	134	262	857	-14,5 (41,5; 23,5)
DSL PTH IRMA	323	638	2108	123,0 (53,1; 188,9)
DSL PTH ELISA	264	523	1734	79,6 (-8,0; 180,9)
Elecsys PTH	161	311	1011	7,3 (-13,8; 80,3)
Immulite 2000 *intact* PTH	212	410	1334	37,8 (37,8; 130,8)
PTH-ACS 180	185	374	1256	18,8 (-9,9; 69,4)
PTH AdviaCentaur	168	342	1154	9,5 (27,6; 55,6)
Intact PTH advantage	174	339	1109	14,6 (-10,4; 72,2)
Ca-PTH IRMA	84	165	543	-44,8 (-65,6; -22,8)
BioIntact PTH advantage	109	214	704	-27,6 (-53,0; 12,5)

25 OH Vitamina D e 1,25 OH2 Vitamina D

L'emivita della 25-OH vitamina D è di 2-3 settimane e la sua concentrazione dipende dalla quantità di ormone che viene rilasciata nel torrente sanguigno. L'emivita della 1,25-$(OH)_2$ vitamina D è di 2-4 ore e la sua concentrazione è circa 100-1000 volte inferiore a quella della 25-OH vitamina D e degli altri metaboliti.

25 OH vitamina D: Il campione è stabile per 120 ore a 2°-8° C, per conservazione prolungata congelare a -20°C. Evitare di congelare e scongelare più volte il campione.

1,25$(OH)_2$ vitamina D: Il campione è stabile per 2 ore a temperatura ambiente, per conservazione prolungata congelare a -20°C. Evitare di congelare e scongelare più volte il campione.

Fattore di conversione

25 OH vitamina D: ng/mL x 2,5= nmol/L
1,25$(OH)_2$ vitamina D: pg/mL x 2,4= pmol/L

Metodologie impiegabili

25 OH vitamina D: RIA, ELISA con estrazione, CLIA diretto
1,25$(OH)_2$ vitamina D: RIA con estrazione

- Altri dosaggi come 1-25(OH)$_2$ Vitamina D, ALP ossea ed osteocalcina sono da riservare a casi più selezionati (rachitismi genetici) e in laboratori con particolare esperienza.

- Vi sono poi markers più specifici, da riservare a situazioni particolari e a casi che debbano iniziare trattamenti potenzialmente lesivi sull'osso (es. terapie corticosteroidee a lungo termine, antineoplastiche e immunosoppressive) o terapie con azione diretta sul metabolismo osseo (es. bisfosfonati) in cui si debba fare un bilancio tra formazione e riassorbimento osseo

Markers del turnover osseo

Derivano sia dall'osso corticale che da quello trabecolare

Riflettono l'attività metabolica dell'intero scheletro

Misurano in modo non invasivo i cambiamenti del turnover osseo

Sono comunemente divisi in **3** categorie:
- marker di riassorbimento osseo
- proteine di regolazione dell'attività osteoclastica
- marker di neoformazione ossea

- I marker di apposizione ossea, oltre alla ALP ossea e osteocalcina (OC), sono la undercarboxylated osteocalcin (ucOC) e procollagen type I C- e N-terminal peptides (P1CP e P1NP).

- I markers di riassorbimento includono deoxypyridinoline, collagen I C- e N-terminal telopeptides (CTX e NTX) , e tartrate resistent acid phosphatase (TRACP) isoforma 5b.

Table I. Markers of bone resorption osteoclast regulatory proteins and their activity in fracture healing

Bone-resorption markers	Source/action	Marker activity in fracture healing
CTX	8 amino-acid fragment from C-telopeptide of type-I collagen Generated by cathepsin-K activity[7]	Rises first week after fracture of the tibial shaft and remains elevated throughout fracture healing[8]
NTX	8 amino-acid fragment from N-telopeptide of type-I collagen Generated by cathepsin-K activity[9]	Not been investigated in fracture healing
ICTP	Carboxy-terminal telopeptide of type-I collagen Released by matrix metalloproteinase[10] Eradicated by cathepsin K activity	Rises first week after fracture of the tibial shaft and remains elevated throughout healing[11-13]
PYD	Form cross-links between mature collagen polypeptides	Peaks 1 to 4 weeks after fracture of the tibial shaft,[14] 1 to 8 weeks after proximal femoral fracture[15]
DPD	Form cross-links between mature collagen polypeptides	Peaks 1 to 8 weeks after proximal femoral fracture[15]
Osteoclast regulatory proteins		
RANKL	Member of tumour-necrosis family, produced by osteoblasts and activated by T lymphocytes	Not been investigated in fracture healing
OPG	Secreted by osteoblasts as a decoy-receptor to bind to RANKL. Down-regulates osteoclast activation and proliferation[21,22]	Not been investigated in fracture healing
TRAcP	Glycoprotein produced by osteoclasts and activated by macrophages/dendritic cells. Acts as phosphatase and generator of oxygen-free radicals	Peaks at 7 days after osteosynthesis in ankle fractures and 2 weeks in tibial fractures[11]
Cathepsin-K	Cysteine protease produced by osteoclasts	Not been investigated in fracture healing

Table II. Markers of bone formation and their activity in fracture healing

| Bone-formation markers	Source/action	Marker activity in fracture healing
PIIINP	N-terminal peptide cleaved from type-III procollagen when it forms type-III collagen	Maximal levels at 2 weeks after ankle fracture and 12 weeks after fracture of the tibial shaft[8,11-13]
PICP	C-terminal peptide cleaved from type-I procollagen when it forms type-I collagen	Peaks 20 to 24 weeks after fracture of the tibial shaft[11,13] Peaks 2 weeks after distal radial fracture remaining elevated at 9 months[24]
PINP	N-terminal peptide cleaved from type-I procollagen when it forms type-I collagen	Maximal at 12 weeks after fracture of the tibial shaft remaining elevated at 24 weeks.[8] Similar results with proximal femoral fractures[15]
OC	Main non-collagenous protein produced by osteoblasts	Elevated at 24 weeks after fracture of the tibial shaft[8,11] Elevated 1 week after distal radial fracture[24]
BSAP	Isoenzyme produced by osteoblasts involved with calcification of skeleton and bone formation	Increased at 4 weeks after fracture of the tibial shaft.[8,11,14,25] Remains elevated at 1 year[14]
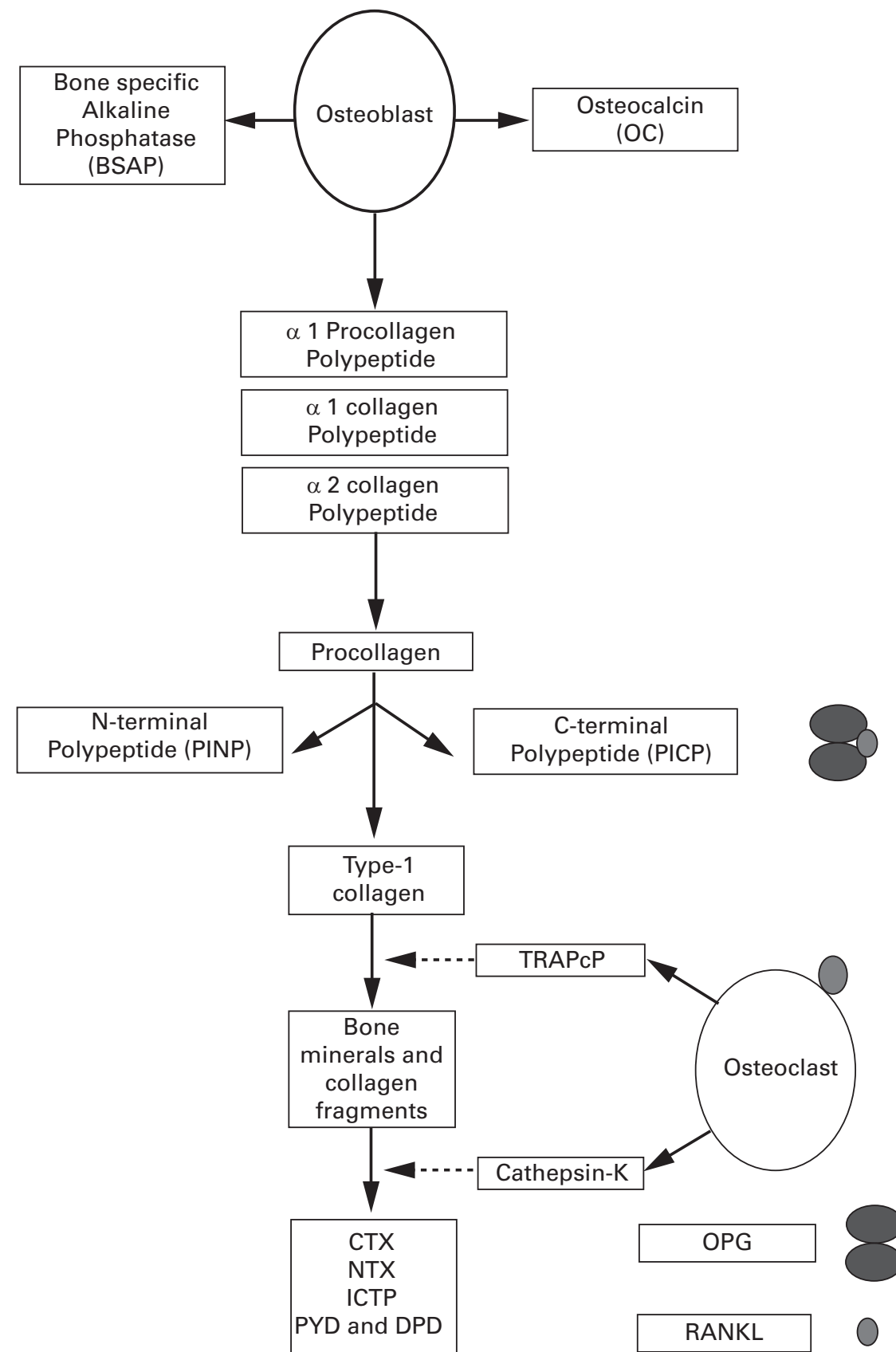
Fig. 1

Diagram showing osteoblastic activity producing BSAP, osteocalcin and type-I procollagen. Procollagen has PINP and PICP molecules cleaved off to form type-I collagen. RANKL and OPG are secreted by osteoblasts. RANKL up-regulates osteoclastic activity and OPG acts as a soluble decoy molecule binding to RANKL and hence causing down-regulation. Osteoclasts, once activated by RANKL, secrete TRAcP which cleaves type-I collagen into fragments.
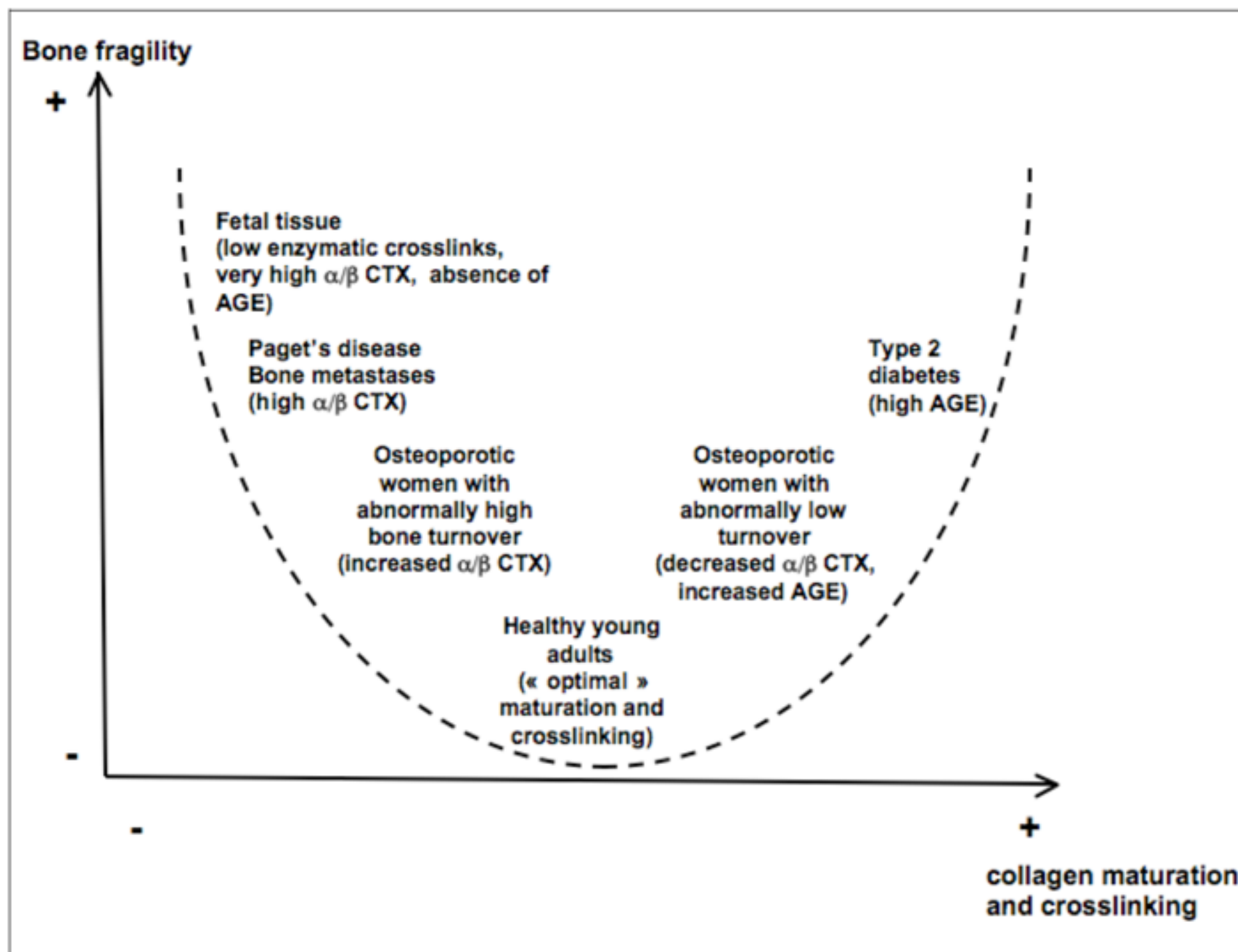
PERSPECTIVES

New Biochemical Markers of Bone Turnover

Patrick Garnero

*INSERM and Synarc, Lyon, France*

Fig. 4: Hypothetical relationship between collagen maturation and bone fragility with age and disease. The α/β CTX ratio reflects isomerization of aspartic acid within the C-telopeptide of the type I collagen $\alpha1$ chain, with a high ratio indicative of a low degree of isomerization. AGE: non-enzymatic Advanced Glycation End products.

- Lo studio del metabolismo osseo del bambino deve tenere conto che lo scheletro è in fase di crescita e che il turnover osseo è generalmente aumentato.

- L'età e lo stadio puberale influenzano lo stato del metabolismo osseo e l'interpretazione dei dati di laboratorio deve tenere conto di questi fattori, per cui esistono curve di riferimento adeguate per età e sesso.

- Ogni laboratorio dovrebbe avere standard di riferimento adeguati sviluppati in proprio

FIG. 1. A, Backtransformed reference curves for bone markers in boys (filled circles) and girls (open circles)

Oc

BALP

ICTP

CTx

TRAP5b

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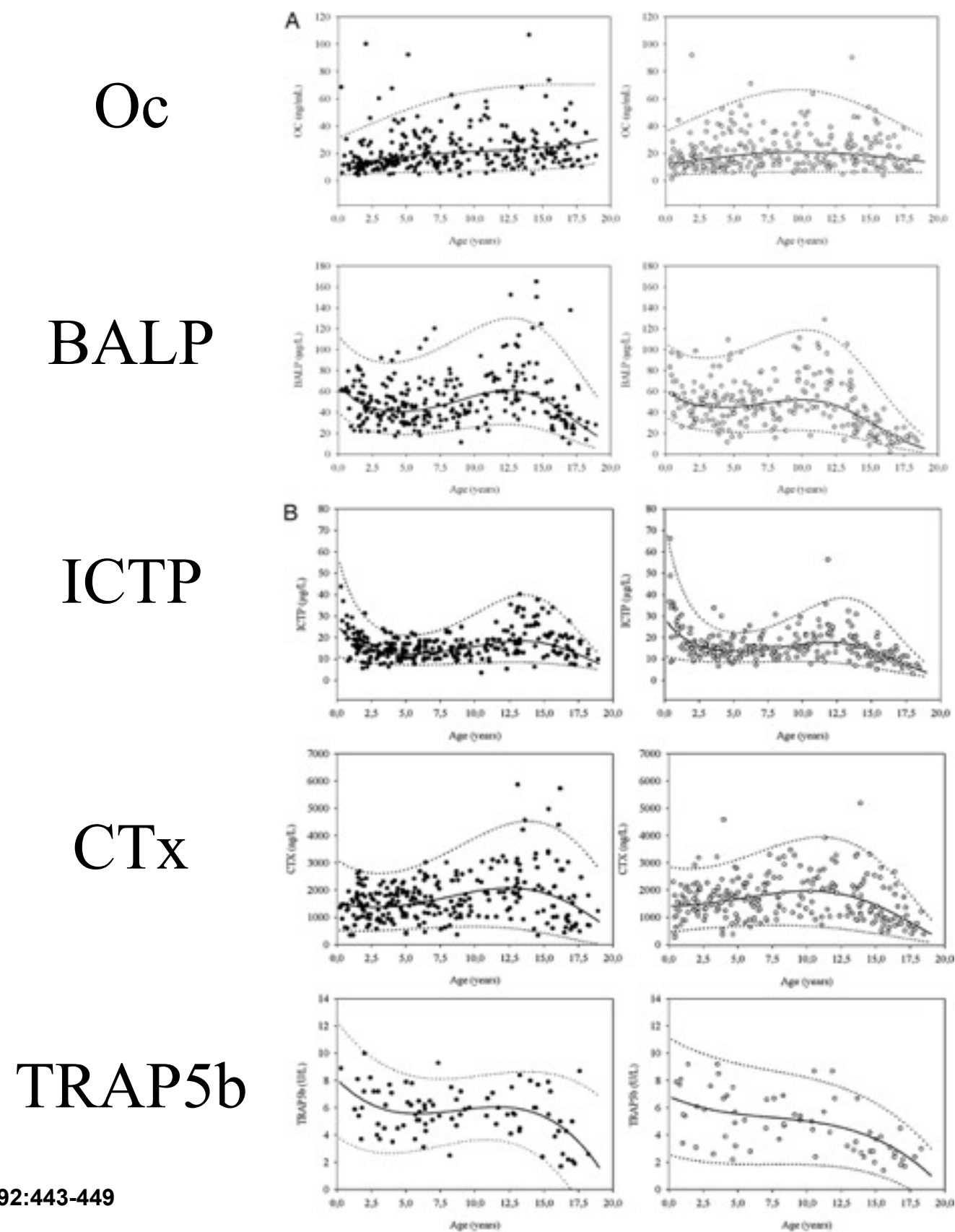
Esami

- Esami di Laboratorio
- Radiografie
  Polso, arti, cranio
- Ecografie
  renale, paratiroidi
- Scintigrafia
  ossea, tessuto paratiroideo